

## The Lancet Commissions



# After asthma: redefining airways diseases

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### Executive summary

Asthma is responsible for considerable global morbidity and health-care costs. Substantial progress was made against key outcomes such as hospital admissions with asthma and mortality in the 1990s and early 2000s, but little improvement has been observed in the past 10 years, despite escalating treatment costs. New assessment techniques are not being adopted and new drug discovery has progressed more slowly than in other specialties.

In this Commission, we aim to provide our view of where we are and where we need to go as a community of clinicians and researchers who tackle the considerable public health problem of asthma. The Commission should not be seen as a comprehensive review but an article that reflects the collective view and opinions of the Commissioners. This Commission is also a call for action to all clinicians involved in the field. The aim of the Commission is to identify entrenched areas of asthma management and treatment in which progress has stalled and to challenge current principles, and the results have been integrated into seven sections.

In the first section of the Commission we argue that our physiology-based classification system for airways diseases is outdated because it provides a restricted view of the heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in patients with asthma. In a 2011 review,<sup>1</sup> Kola and Bell discussed poor progress in new drug discovery and stated that “Many common human diseases are still diagnosed as if they are homogeneous entities, using criteria that have hardly changed in a century...the treatment for diseases that are diagnosed in this way is generic, with empiricism as its cornerstone”, which is particularly pertinent. Our simplistic concept of disease, and the assumption that all asthmas are the same, nearly resulted in the considerable clinical benefits of corticosteroids<sup>2</sup> and mepolizumab, a monoclonal antibody that targets the type 2 cytokine interleukin 5,<sup>3</sup> being missed. We believe that these entrenched concepts are the most important causes of the stagnation in key clinical outcomes observed in the past 10 years despite ever increasing spending on asthma treatment.<sup>4</sup>

We suggest that the only way we can make progress in the future is to be much more clear about the meaning of the labels used for asthma and to acknowledge the assumptions associated with them. Airways diseases should be deconstructed into traits that can be measured and, in some cases, modified (ie, treatable traits), and

which are set in the context of social and environmental factors and extrapulmonary comorbidities. An important catalyst for this change has been the discovery of simple and clinically accessible measures of one of the most influential and treatable traits: eosinophilic airway inflammation.<sup>5</sup> Stratification using these measures identifies patients who are at risk of adverse outcomes and are likely to benefit from inhaled corticosteroids much more precisely than traditional measures and disease labels,<sup>6</sup> and the use of these biomarkers to stratify patients has been instrumental in successful new drug development.<sup>7,8</sup>

The second section considers how this new approach could be operationalised in all health-care settings. We call for a fundamental rethink of the current guidelines with greater emphasis on traits that can be measured and treated and less emphasis on arbitrary disease labels. One result will be that inhaled corticosteroids are used in a more targeted, biomarker-directed, and hopefully, more efficient way. The Commissioners considered at length the risk that moving from an approach that focuses on more inhaled corticosteroids in more lungs to one that focuses on more inhaled corticosteroids in the right lungs, might jeopardise the substantial improvements in key outcomes seen between 1990 and 2005 using the former approach. Importantly, the long-term safety of withholding inhaled corticosteroids in patients with low biomarkers of eosinophilic (or type 2) inflammation is unclear. Our pragmatic solution is the use of as-required combination low-dose inhaled corticosteroid and rapid onset  $\beta_2$ -agonist inhalers as the default reliever option so that patients with episodic symptoms and airway inflammation are more likely to receive inhaled corticosteroids at a crucial time, while acknowledging that this approach needs to be tested. We suggest that inhaled corticosteroid treatment is not escalated beyond this point unless biomarkers of type 2 inflammation are increased. Substantial rationale exists for this approach, which is supported by evidence from clinical trials.<sup>9</sup> Once established on treatment, monitoring needs to improve from questions about how the patient is feeling to 21st century real-time use of biomarkers and tools to facilitate risk stratification and treatment adherence.

In the third section, we consider the implications of this approach regarding the development and evolution of airway diseases through infancy, childhood, and adult life. Much more needs to be done to enable this proposed deconstruction of airway disease in non-invasive ways in

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patients of all ages. Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network might still be difficult to predict, partly because these mechanisms are superimposed on a system that is developing during childhood and declining during senescence. To make sense of this additional complexity, the use of the correct principles and concepts is important. Predominantly, a reductionist approach is used to identify involved mechanisms and treatable components, which can lead to novel drug development or therapeutic concepts. However, to understand how these mechanisms interact, how asthma phenotypes evolve during childhood, or how stable phenotypes remain over time, novel methods of systems biology need to be implemented to address this complexity. We stress the importance of the complementary use of the reductionist and system-based approach, and ensuring that the right method is used for the right question. We also need to move on from current birth cohorts, informative though these have been, if the fundamental causes of asthma are to be addressed, and we need to move beyond satisfaction with the existing situation, towards the ambition of preventing or curing asthma.

When considering asthma treatment clinicians usually focus on established asthma, rather than the fundamental underlying causes. This approach has set the agenda for asthma as a chronic disease that should be controlled rather than cured. The fourth section questions whether the inevitable progression from intermittent early childhood wheeze to persistent asthma in the adolescent years and a subsequent lifetime of therapeutic drug dependence, can be modified. We call for no more me-too medicines but a commitment to develop treatment approaches that focus on prevention and cure.

The fifth and sixth sections discuss two areas in which we believe that real and important progress is at our fingertips: the prevention of asthma attacks and improved treatment for patients with severe asthma. We advocate consideration of asthma attacks as a sentinel event that should prompt a thorough re-evaluation of asthma management in the patient, and we propose a re-thinking of current one-size-fits-all approaches to treatment and secondary prevention of attacks. Prevention of attacks of asthma are one of the most tractable aspects of airway disease management, being highly responsive to better control of lower airway inflammation, whether achieved with targeted corticosteroid treatment<sup>10,11</sup> or with highly selective biological drugs that inhibit type 2 inflammation.<sup>12</sup> The use of as-required combination corticosteroid and rapid onset  $\beta_2$  agonist inhaler therapy as the default reliever option is likely to provide an effective solution for the small number of patients with episodic, but high-risk disease, who feature consistently in asthma mortality statistics. Using biomarkers of type 2 inflammation results in better stratification of risk and adoption of these biomarkers in the assessment of mild and moderate

asthma will align well with an approach that is of acknowledged value in severe asthma;<sup>6,7,13</sup> however, we must use the tools of modern molecular and systems biology to identify better biomarkers of risk and treatment response. The use of these biomarkers will be essential to take advantage of the increasing numbers of new treatments that selectively inhibit type 2 inflammation.

The final section calls for better clinical, epidemiological, and basic science research. Future clinical trial populations, patient cohorts, and animal models should be selected on the basis of possession of the trait we are seeking to modify or study, rather than arbitrary diagnostic labels (particularly those without any precision, such as so-called doctor-diagnosed asthma), and an outcome measure should be selected that is associated with this trait and relevant to patients. Using models because they are available (eg, systemic sensitisation of mature mice) rather than because they represent disease realities, needs to change. This approach will inform rather than obscure the identification of new treatable traits. Regulatory authorities such as the Food and Drug Administration, reviewers of manuscripts, and grant funding agencies are rightly concerned that trials are done in well defined populations, but should these populations have the diagnostic characteristics of an arbitrary condition (ie, asthma or chronic obstructive pulmonary disease [COPD]) that are defined by current guidelines? We think not, but we must ensure that all stakeholders are aligned to any proposed change.

Perhaps ambitiously, we propose a revolution in thinking about asthma that is generalisable to all airways diseases, which, alongside the undoubted importance of optimum delivery of the best care to each patient, will deliver real precision asthma medicines, dissecting airways diseases into component parts and addressing each in turn, stratified by risk. We believe that the approach we advocate—which takes a step back from traditional disease labels—will change clinical routine, diverting the medical community away from a diagnostic and therapeutic standstill, resulting in a new system that will be valuable in epidemiological and interventional studies. This approach should increase the likelihood that we will unravel the key components of asthma and, eventually, develop better medicines and achieve better outcomes for our patients. We hope this new approach will add momentum to the recent encouraging progress in new drug discovery and, as did the first asthma guidelines published 27 years ago,<sup>14–17</sup> lead to a decade or more of improved outcomes. We conclude the Commission with seven key recommendations and summarise our views on how these could be developed to benefit patients with asthma (panel 1).

## Introduction

Wherefore is this disease different from all other diseases?

Maurice Pappworth<sup>18</sup>

**Panel 1: Summary of recommendations****A revolution in thinking about asthma, generalisable to all airways diseases, and delivering precision medicine**

- Use the term asthma solely as a descriptive label for a collection of symptoms, with no assumptions about pathophysiology
- Deconstruct airway disease into component parts before planning treatment, with a focus on traits that are identifiable and treatable (ie, treatable traits)
- A new approach to the management and monitoring of patients with airway disease whereby the two dominant treatable traits (risk of attacks associated with eosinophilic airway inflammation and symptoms as a result of airflow limitation) are assessed and managed individually, resulting in a precision medicine approach that is applicable in non-specialist care
- This precision medicine approach also encompasses the investigation and treatment of overlapping disorders, comorbidities, and lifestyle and environmental factors

**Move beyond a disease control-based approach for asthma treatment**

- Direct resources toward primary prevention strategies (asthma prevention) and disease modifying interventions (asthma cure)

**Emerge from our age-associated and discipline-associated silos**

- Consider airway disease in the context of the developmental trajectory from birth to old age
- Use a reductionist approach to identify mechanism and treatable traits and a systems biology approach to address the complexity of the interaction between different traits and ageing
- Regulators should enforce existing guidelines for mandatory testing plans for children as part of licensure process for new asthma drugs

**Test before treatment**

- Move away from the current no-test culture in clinical practice
- Early detection of poor lung function by spirometry in early adulthood
- Alignment of testing with a highly focused and effective educational campaign on the dangers of smoking

**Zero tolerance for attacks**

- Replace the inadequate terms exacerbation or flare-up with attack
- Precision medicine rather than a one-size-fits-all approach to treatment and secondary prevention of attacks
- Development of a risk score and incorporation into every day clinical practice

- Lobby patient organisations to do more to identify and advertise high-risk periods and provide targeted and effective patient advice
- Replace as-required short-acting  $\beta_2$  agonists with combination inhaled corticosteroid and fast-acting  $\beta_2$  agonist as reliever therapy in patients with episodic symptoms, with no escalation of inhaled corticosteroid dose unless biomarkers of eosinophilic disease and inhaled corticosteroid responsiveness are present

**Make the most of new treatment opportunities in severe disease**

- Move from a traditional disease category, symptom, and lung function-based assessment of treatment need and response to one in which decisions are driven by the presence and responsiveness of the relevant trait
- Develop tests capable of identifying poor adherence and treatment approaches capable of improving adherence
- Ensure biological drugs are used effectively in individual carefully characterised patients
- Identify the best biological drugs for individual patients by collating data from phase 2 and 3 clinical trials and carefully collecting post-registration patient data with the goal of identifying responsive subgroups, with prospective validation of the findings

**Better research**

- Deliver more treatment to the right lungs rather than more treatments to more lungs by working in collaboration with the pharmaceutical industry to ensure that future clinical trials establish not only treatment efficacy and safety but identify definable subgroups who derive particular benefit from treatment
- Select trial populations on the basis of possession of the characteristic we are seeking to modify rather than arbitrary diagnostic labels
- Ensure that regulatory authorities and patient groups are aligned to any proposed change
- Stop assuming that asthmas across the globe are the same disease
- Move from observational studies to intervention studies, defining the components we are interested in and measuring them with much more precision, adopting novel adaptive research designs when necessary
- Animal models that are closer to real life, offering us the best prospect of understanding the complex interplay between different inflammatory pathways, defining why aberrant inflammatory pathways perpetuate and identifying preventive strategies

The first asthma guidelines were written 27 years ago,<sup>14–17</sup> and asthma was identified as a disease associated with airway inflammation. These guidelines led to the widespread use of inhaled corticosteroids instead of

repeated and even regular doses of short-acting  $\beta_2$  agonists as primary treatment, with great benefit to many patients (figure 1). However, progress against key outcomes has slowed over the past 10 years despite

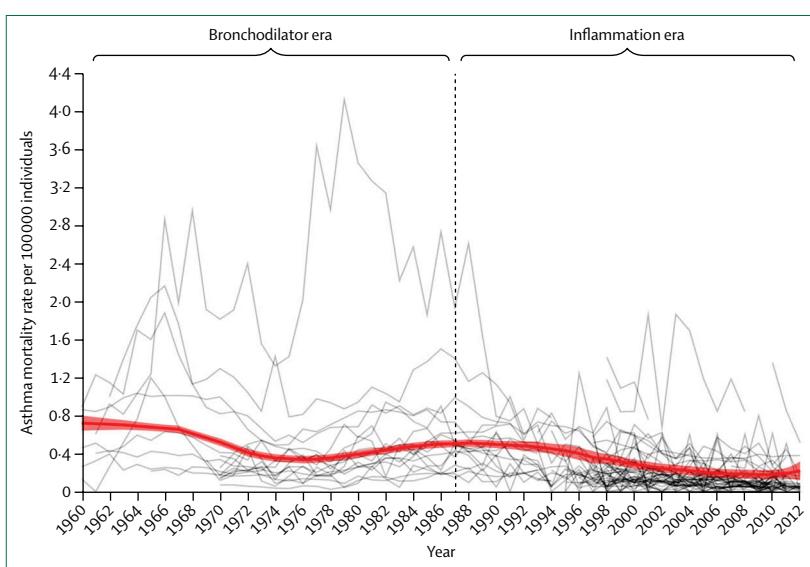
increased spending on treatments<sup>20</sup> and has not matched that enjoyed by other specialties.<sup>21</sup> We believe that the most important cause of this stagnation is a continued reliance on outdated and unhelpful disease labels, treatment and research frameworks, and monitoring strategies, which have reached the stage of unchallenged veneration and have subsequently stifled new thinking.

The notion that a rheumatologist diagnosing arthritis or a haematologist diagnosing anaemia, would generically treat patients without determining the specific cause and type of disease in the 21st century is absurd. Yet, the umbrella term asthma continues to be applied to a disparate group of conditions characterised by varying degrees of airflow limitation (both fixed and labile), different (or no) patterns of inflammation, contributions from bacterial and viral infections that vary over time, an oversensitive cough reflex, and mucus hypersecretion. Despite an increased number of research papers studying the pathology of asthma and identifying fundamentally different patterns of disease, especially airway inflammation, this stereotypical label remains, and asthma therapy has progressed little in the past 20 years, with Rosenthal<sup>22</sup> summarising that “therapy still comprises a blue and a brown inhaler (the latter of which usually left to gather dust in the bathroom cabinet), measuring the urinary cotinine and looking menacingly at the pet cat”. This simplistic chain of reasoning has become that wheeze or cough represents asthma, which must equal eosinophilic airway inflammation and the subsequent need for prescription of inhaled corticosteroids. If symptoms persist, this means that eosinophilic inflammation is refractory and more treatment must be given.

Concerns about outdated disease taxonomy were expressed in 1958<sup>23</sup> and again in a *Lancet* editorial<sup>24</sup> published in 2006, but little has changed. However, the development and clinical use of non-invasive methods to assess airway inflammation has been a catalyst for change.<sup>5</sup> These techniques have shown that asthma and other airway diseases consist of a heterogeneous mix of pathologically distinct processes that are poorly represented by the existing physiological and symptom-based classification system<sup>6,7,25</sup> and thus, have enabled a new precision medicine type approach to management. Type 2 (or eosinophilic) airway inflammation has emerged as particularly important because it is readily recognisable and is associated with risk of attacks that can be prevented with corticosteroid treatment.<sup>6</sup> Management guided by non-invasive measures of eosinophilic airway inflammation rather than traditional symptom and lung-function based measures results in better outcomes and more economical use of treatment,<sup>10,11,26,27</sup> and the same basic approach works well irrespective of the diagnostic label. Moreover, biological drugs that specifically inhibit eosinophilic airway inflammation by blocking the type 2 cytokine interleukin 5, and interleukin 13 and interleukin 4 have been shown to have important beneficial effects when given to adult patients with airways disease and this pathology, but not when evaluated in all patients with asthma.<sup>3,12,28–31</sup> Clearly, a new form of stratification of airway disease will be essential to exploit the opportunities provided by these new biological treatments. The absence of eosinophilic airway inflammation is also important in patients with asthma because it indicates that inhaled corticosteroids should not be escalated, and new treatment possibilities should be considered.

Our concern is that continued reliance on an approach that oversimplifies and overgeneralises a complex and heterogeneous syndrome (asthma) will result in other pathogenically important and tractable mechanisms being missed. New thinking is needed and we hope that this Commission will stimulate this. The Commission is based on the assumption that asthma is no more a 21st century diagnosis than arthritis,<sup>32</sup> and will attempt to liberate this mix of airway diseases from the protective but restricting diagnostic label of asthma to reflect the clinical and pathological heterogeneity of different asthmas and allow the management of these diseases to progress to the next level.

The Commission asked experts in various fields, linked by a common expertise in asthma, to consider where our concept of asthma and management of the disease should be in the 21st century, and how best to achieve these goals. An important early goal was to move out of age-associated (paediatric, adult), discipline-associated (basic science, epidemiology, and clinical research), disease-associated, and nationality-associated silos and attempt to think in a more collaborative way. Our list of Commissioners, all acknowledged experts in their respective fields, were chosen to reflect this goal. The Commissioners met in



**Figure 1:** Crude asthma mortality rates between 1960 and 2012 for individuals aged 5–34 years in 46 countries during the bronchodilator and inflammation eras of asthma management

The association between the anti-inflammatory era and improved outcomes, and the flat-line with regard to further improvements between 2005 and today, is evident. The red lines indicate the locally weighted scatter plot rates after scatterplot smoothing with 90% confidence intervals, weighted by country population. The grey lines represent the rates of individual countries. Reproduced from Ebmeier et al.<sup>19</sup>

person on three occasions between November, 2014, and September, 2016, and had numerous teleconferences. Each Commissioner identified ten areas in which they felt progress was most pressing. These points for progress were organised into seven themes and working groups were assembled to discuss each (panel 2). The Commissioners collectively felt that an entirely independent view was required and, for this reason, no sponsorship was sought and no payments were made for expenses. Our aim was to identify entrenched areas of asthma management and treatment in which progress has stalled and to challenge current thinking. Each theme addressed the same two questions: where are we now and where do we want to go?

### **Changing how we think about airways diseases**

#### **Changes in the concept of asthma over the years**

Asthma has been recognised since antiquity. The word asthma is derived from the Greek  $\alpha\sigma\theta\mu\alpha$ , meaning a short-drawn breath, hard breathing, or death rattle (figure 2) and thus was, at the outset, a term used to describe a complex of symptoms rather than a specific disease entity. Early pathogenic models suggested that airflow to the body was impeded by phlegm from the brain lodging in the lungs. These models also indicated an association between the condition and environmental factors, including climate and geographical areas. Sir John Floyer,<sup>38</sup> who had asthma, provided the first modern publication about the disease in 1698 (figure 2), and identified bronchial constriction as a cause of wheezing. He was also the first to describe asthma attacks and potential triggers by providing a first-hand account of his own experiences. Henry Hyde Salter,<sup>39</sup> also an asthmatic, provided a more formal definition of asthma in the late 19th century (figure 2) and stated that "if it is at all severe and its attacks frequent, cannot long exist without inflicting permanent injury to the lungs". This definition likely represents the first time that asthma was associated with airway damage, a process now known as airway remodelling. Salter's description of the burden of asthma attacks remains the most vivid and compelling account of the effect of this condition (panel 3).

Francis Rackemann did a detailed longitudinal clinical study of asthma in the first half of the 20th century and was the first to highlight the heterogeneity of asthma.<sup>40</sup> He commented that "surely it is hard to believe that the wheeze that comes to the young school girl for a day or two in the ragweed season is the same disease as that which develops suddenly in the tired business man or in the harassed housewife and pushes them down to the depths of depletion and despair. The problem is still wide open: the approach is not at all clear".<sup>40</sup> Rackemann described two clinical asthmatic phenotypes: extrinsic asthma, thought to be due to allergens from outside the body and associated with younger age of onset, environmental triggers, atopy and the presence of other allergic diseases; and intrinsic asthma, due to factors

#### **Panel 2: Contributions to the Commission**

##### **Changing how we think about airways diseases (page 9)**

Ian D Pavord, Richard Beasley, Alvar Agusti, Peter Gibson, Francine M Ducharme, Guy Marks, Guy Brusselle, Andy Bush

##### **Beyond guidelines: operationalisation of individualised treatment in different health-care settings (page 21)**

Richard Beasley, Ian D Pavord, John V Fahy, Sally Wenzel, Liam G Heaney, Elisabeth Bel, Heather J Zar, Marc Humbert, Andy Bush

##### **Wheezing illnesses across the ages (page 27)**

Urs Frey, Andy Bush, Alvar Agusti, Paul Cullinan, Francine M Ducharme, Peter D Sly, Fernando D Martinez, Erika von Mutius

##### **Beyond palliative care: towards prevention and cure (page 32)**

Patrick G Holt, Andy Bush, Peter D Sly, Erika von Mutius, Gary P Anderson, Clare M Lloyd, Paul Cullinan, Fernando D Martinez, Adnan Custovic

##### **Attacking asthma attacks (page 35)**

Ian D Pavord, Andy Bush, Richard Beasley, Peter Gibson

##### **Getting serious about severe disease (page 36)**

Liam G Heaney, Sally Wenzel, Elisabeth Bel, Marc Humbert, Guy Brusselle, Ian D Pavord, Andy Bush

##### **Improvement of research (page 40)**

Clinical trials  
Richard Beasley, Ian D Pavord, Andy Bush

##### **Integration of epidemiology, genetics, and translational research**

Richard Beasley, Erika von Mutius, Paul Cullinan, Fernando D Martinez, Guy Marks, Urs Frey, Heather J Zar, Adnan Custovic, Paul Cullinan, Peter D Sly

##### **Animal models and basic immunology**

Clare M Lloyd, Guy Brusselle, Patrick G Holt, John V Fahy, Gary P Anderson

intrinsic to the body associated with older age at onset and the absence of atopy.<sup>40</sup>

The association between asthma and variable airflow obstruction was formally recognised soon after spirometry was introduced by Hutchinson<sup>41</sup> in the 1840s and the association between airflow obstruction and a low forced expiratory volume in 1 s to vital capacity ratio was described by Tiffeneau<sup>42</sup> in the 1940s. Bronchodilator reversibility has emerged as the diagnostic test of choice although the validity of this test has never been properly addressed<sup>43</sup> nor has it been acknowledged that this test provides no information about the presence and nature of underlying airway inflammation. Bronchodilator treatments, including epinephrine, anticholinergics, methylxanthines, and inhaled  $\beta$  agonists were all introduced in the first half of the 20th century and, early in the second half of the century, systemic

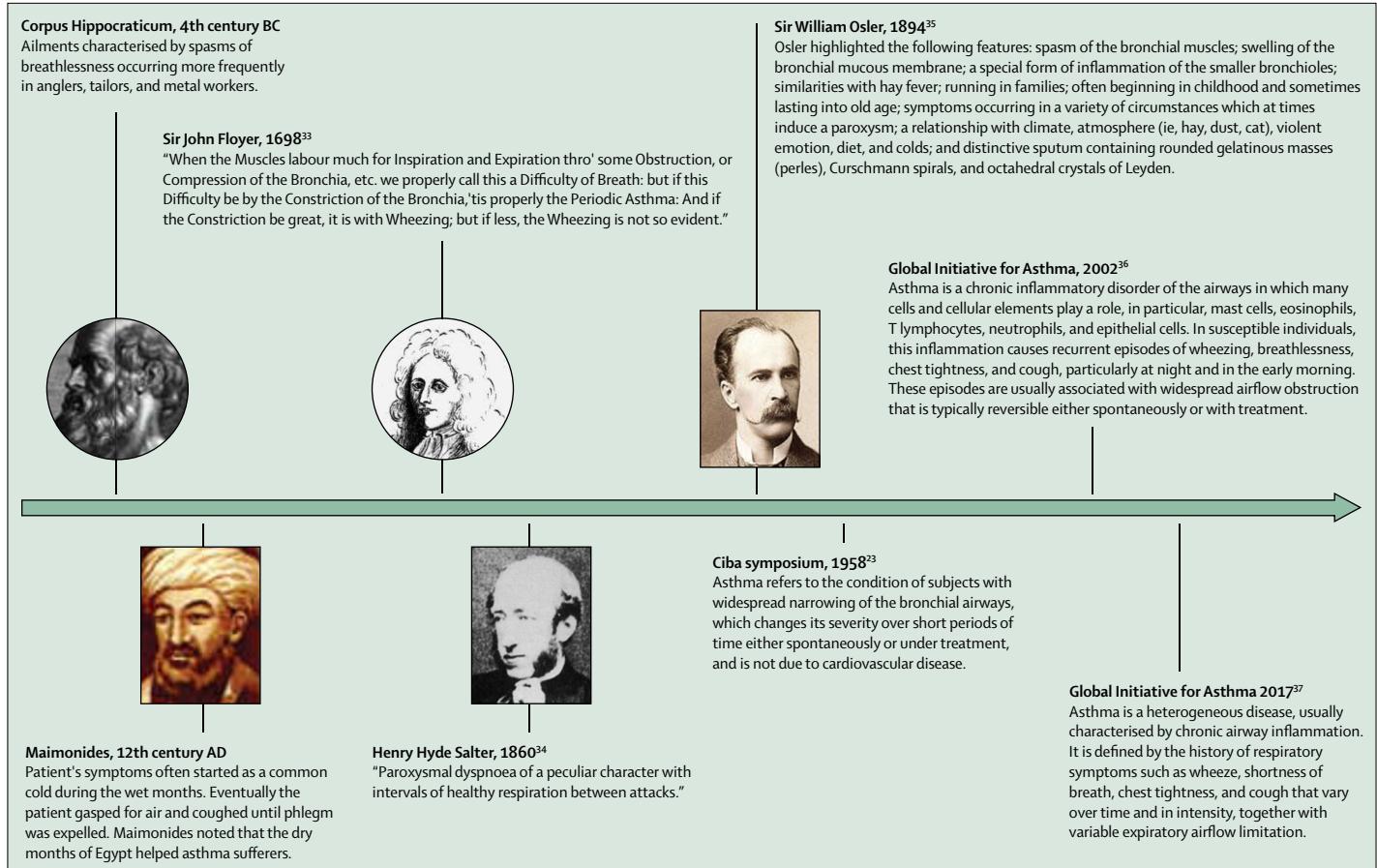


Figure 2: Asthma definitions throughout history

corticosteroids were identified as a potentially useful treatment. The introduction of systemic corticosteroid treatment in the 1950s in the UK was not entirely straightforward because an early and influential clinical trial<sup>44</sup> sponsored by the Medical Research Council showed little efficacy and highlighted a high potential for systemic toxicity. The physician Harry Morrow-Brown<sup>2</sup> was surprised by these negative findings and subsequently used his medical student microscope to show that systemic corticosteroids had clear efficacy in patients with asthma who had eosinophils present in their sputum smear but not in those without. In the 1970s, he used a similar method of patient selection to show that inhaled beclometasone dipropionate was an effective topical treatment when administered by aerosol and that treatment mitigated the adverse effects of oral corticosteroids by allowing a considerable number of patients to withdraw this treatment without loss of asthma control.<sup>45,46</sup> This work was widely ignored over the next 50 years, but in retrospect was pioneering and important because it showed for the first time that asthma is associated with different patterns of airway inflammation and demonstrated that it is clinically important to distinguish them.

The heterogeneity of wheezing disorders has long been appreciated in paediatrics, and the numerous studies can only briefly be summarised here. In the 1960s, both Selander<sup>47</sup> and Fry<sup>48</sup> astutely observed that episodes of infant wheeze were temporally associated with outbreaks of viral infection in the community, but these infants with wheeze did not develop asthma in childhood. General paediatrician Jeremy Cogswell further investigated this observation in a small but highly influential study<sup>49,50</sup> showing that early exposure to house dust mite was of great importance to the development of early childhood asthma, but was not associated with wheeze in infancy. Long-term studies have confirmed that there are many different patterns of wheeze. The Melbourne cohort,<sup>51</sup> which has reached the sixth decade with around 75% retention, tracked lung function throughout the study period and showed that patients who just wheezed with viral colds (wheezy bronchitis as it was initially described) had normal lung function throughout the life course, but children with asthma, and particularly severe asthma, had permanent obstructive defects. Indeed, the children with severe asthma had a more than 30 times higher risk of COPD than children without asthma, and children with severe asthma had the worst lung function at

age 10 years.<sup>51</sup> The clinical differences between patients who wheeze with viral colds and patients with atopic childhood asthma have been confirmed by physiological and pathological differences, although these patterns of wheeze have long been appreciated to be dynamic and show developmental changes.<sup>52</sup>

A classical cohort study was done in Tucson, AZ, USA,<sup>53</sup> which followed babies from birth and initially reported on wheeze at ages 3 and 6 years. The timing of study visits meant that only four wheeze phenotypes could be discerned: never wheeze, transient early (age 0–3 years only), persistent (age 0–6 years), and late onset (age 3–6 years), with different characteristics and evolution over time of lung function. Mathematical modelling in large cohorts with more datapoints or information from health-care records (ALSPAC, PIAMA, KOALA, Dunedin, Manchester, Rotterdam)<sup>54–60</sup> have discerned more phenotypes, concluding that subtypes of childhood wheezing can be identified on the basis of the temporal pattern of wheezing. However, important differences were observed between phenotypes identified in different cohorts using different techniques and data sources, and the use of techniques such as latent class analysis supported the need to move beyond the presence or absence of individual symptoms when assessing airways diseases in childhood.<sup>61</sup> These studies have identified numerous potential risk factors for asthma onset, including maternal asthma<sup>62</sup> and smoking in pregnancy,<sup>63</sup> mode of delivery,<sup>64</sup> low birthweight,<sup>65</sup> impaired lung function<sup>66,67</sup> and airway hyper-responsiveness shortly after birth,<sup>68–70</sup> and the importance of early microbiological exposures.<sup>71</sup> Additionally, just as it has long been appreciated that all wheeze is not equal, different patterns of atopy, with differing significance have emerged.<sup>58,72–75</sup> Thus, the combination of sensitisation to multiple allergens and persistent wheeze with acute attacks is most predictive of a long-term adverse outcome.<sup>59,74,75</sup> The differences between the factors that initiate atopic asthma and those that propagate the asthmatic condition have been acknowledged. Three randomised controlled trials<sup>76–78</sup> of the early initiation of inhaled corticosteroids in infants at risk for the development of asthma have reported relieved symptoms, but have shown no effect of this treatment on the natural history and progression of wheezing, and the few studies that have investigated the pathology of infant wheeze have shown no eosinophilic inflammation in most patients,<sup>79</sup> although properly administered inhaled corticosteroids are an excellent suppressive treatment for recurrent or persistent asthma with eosinophilic airway inflammation.

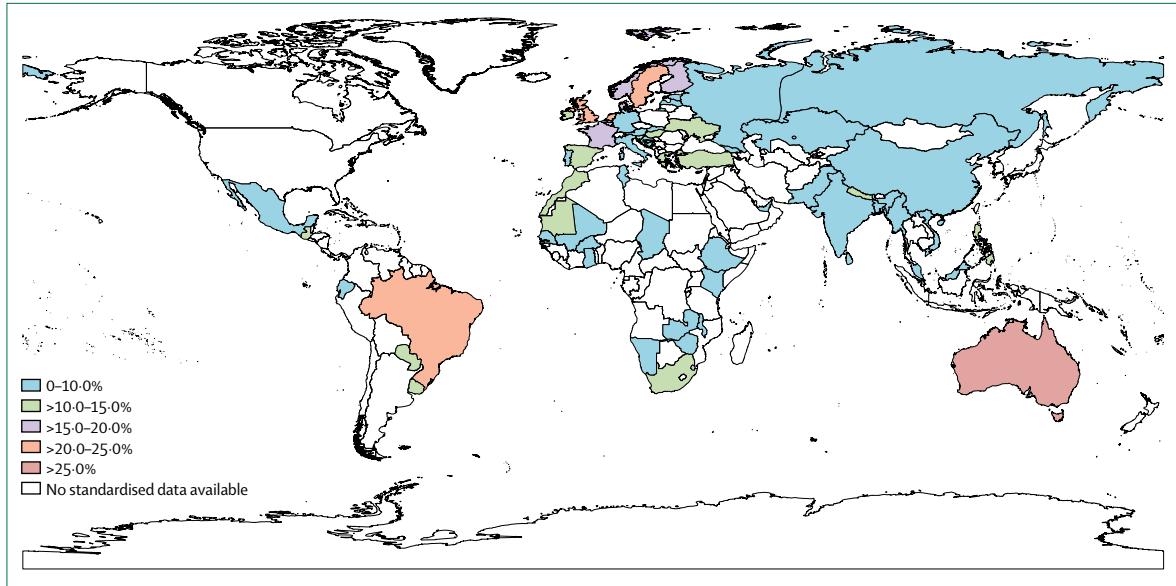
Over the past 50 years, two main eras of asthma management have been identified, each lasting about 25 years: the bronchodilator era, which began with the introduction of increasingly selective inhaled  $\beta_2$  agonists in the mid-1960s and focused on airway hyper-responsiveness as the key pathophysiological abnormality; and the anti-inflammatory era, which began in the late

### Panel 3: Henry Hyde Salter's description of asthma and its effect on the individual<sup>34</sup>

“...but not only is asthma not an uncommon disease, but it is one of the direst suffering; the horrors of the asthmatic paroxysm far exceed any acute bodily pain; the sense of impending suffocation, the agonizing struggle for the breath of life, are so terrible that they cannot even be witnessed without sharing in the sufferer’s distress. With a face expressive of the intensest anxiety, unable to move, speak, or even make signs, the chest distended and fixed, the head thrown back between the elevated shoulders, the muscles of respiration rigid and tightened like cords, and tugging and straining for each breath that is drawn, the surface pallid or livid, cold and sweating—such are the signs by which this dreadful suffering manifests itself...he only knows that a certain percentage of his future life must be dedicated to suffering; he cannot make an engagement except with a proviso, and from many occupations of life he is cut off; the recreations, the enjoyments, the indulgences of others are not for him; his usefulness is crippled, his life is marred; and if he knows anything of the nature of his complaint, he knows that his suffering may terminate in a closing scene worse only than the present.”

1980s, when more aggressive use of inhaled corticosteroids was encouraged and airway inflammation was seen to be of central importance (figure 1). Despite no clear evidence of a correlation between inflammation and airway responsiveness, and the differential response of each to different treatments,<sup>80</sup> the myth that airway inflammation was the origin of all asthma troubles was sedulously cultivated. The initial bronchodilator era was perhaps the first to offer patients with asthma a reasonable quality of life and some degree of control of their symptoms, but was associated with a progressive increase in hospital admissions for acute severe asthma, and an increase in mortality from asthma in many countries. This increased mortality occurred in spikes, compellingly linked to overuse of non-selective  $\beta$ -agonist or high-dose poorly selective  $\beta_2$ -agonist inhalers<sup>81–83</sup> (figure 1). Underuse of inhaled corticosteroids has also contributed to asthma deaths, and depressingly still does.<sup>84</sup> This association between underuse and mortality, and the increasing recognition that airway inflammation was commonly seen even in patients with mild asthma,<sup>85</sup> fuelled the second (anti-inflammatory) era. However, over-reliance on inhaled  $\beta_2$  agonists still contributes to asthma deaths.<sup>86</sup>

Increased use of inhaled corticosteroids was more difficult to implement than the use of  $\beta_2$  agonists, partly because treatment had a less rapid and therefore less obvious effect on symptoms. Guidelines<sup>14–17</sup> were used to encourage patients and prescribers to introduce inhaled corticosteroids earlier and patient education with multidisciplinary input was employed to encourage continued adherence with treatment once a symptom response had occurred. The anti-inflammatory era was



**Figure 3: Prevalence of symptoms of asthma among individuals aged between 18 and 40 years worldwide (World Health Survey 2002–03)<sup>92</sup>**  
Reproduced from To et al,<sup>93</sup> by permission of To and colleagues.

associated with a substantial reduction in hospital admissions with acute severe asthma and mortality from acute asthma, particularly between 1990 and 2005 in children (figure 1). Corticosteroids do not totally obliterate acute bronchodilator reversibility; a third of patients in the Brompton severe asthma registry<sup>87</sup> had reversible airflow obstruction despite an injection of triamcinolone. Evidence<sup>88,89</sup> indicated that combinations of inhaled long-acting  $\beta_2$  agonists and inhaled corticosteroids resulted in superior outcomes for many patients. However, worryingly, at least in children and despite the complete absence of any evidence, combination therapy is commonly prescribed as first-line prevention. More worryingly, long-acting  $\beta_2$  agonists can be prescribed as a single therapy, despite compelling evidence that people use them without concomitant inhaled corticosteroids, which increases the risk of asthma deaths.<sup>90</sup>

Concerningly, progress against key outcomes has stalled in the past 10 years and preventable deaths continue to occur with depressing regularity despite increased investment in asthma treatment. This stagnation could be explained partially by variations in practice, because marked regional and international differences exist in these outcomes, partly associated with access and affordability of asthma therapy, and variations in asthma symptom prevalence<sup>91,92</sup> (figures 1, 3). In Finland, a well coordinated and highly effective national campaign focusing on asthma control resulted in a substantial reduction in hospital admissions due to acute severe asthma.<sup>94</sup> However, although the overall approach was found to be cost-effective, treatment-associated costs were considerable, and the guideline and self-management approach that were the cornerstone of the Finnish

approach have been more difficult to implement elsewhere. A more fundamental concern is that our current one-size-fits-all approach to management cannot be safe and deliver better outcomes to everyone, even despite greatly increasing treatment costs, unless our diagnostic and management frameworks are optimised.

#### Where are we now?

##### *Definition and basic concepts*

The Global Initiative for Asthma 2002 definition<sup>36</sup> of asthma (figure 2), the most widely used definition of the disease, is a lengthy description of pathological, physiological, and clinical features that encompass the major disease characteristics (airway hyper-responsiveness, structural changes to the airways or airway remodelling, disordered mucosal immunity, and chronic airway inflammation). The latest 2017 definition<sup>37</sup> (figure 2) is less descriptive and moves away from these features but, nevertheless, they are still commonly highlighted as important.

To include abnormalities in airway physiology, airway structure, and airway immune function as part of the definition of asthma, these abnormalities need to be well-defined, homogeneous, universally present, causally linked, and readily measurable: the reality is that they are none of these. Although abnormalities in airway physiology can be measured, abnormalities in airway structure, or airway immune function cannot. These differences present a problem because promising treatment approaches for the abnormal airway response to viral infection<sup>95</sup> might not succeed until new techniques are available to assess this component. Similarly, improving airflow limitation is an important goal of

**Panel 4: Disadvantages of relying on measures of airflow limitation to diagnose asthma****Little consensus exists on how to demonstrate variable airflow restriction**

Definitions of abnormality are not closely associated with the normal range for that measure (ie, bronchodilator reversibility). Moreover, the measurement characteristics of different tests are not well studied<sup>96</sup> so the interpretation of abnormal findings is difficult. Most studies compare test findings in patients with asthma and normal controls. This information is not that helpful in clinical practice whereby the clinical question is whether a symptomatic patient has asthma or an alternative explanation for their symptoms. Some tests (eg, peak expiratory flow variability) have been shown to be grossly abnormal in patients with pathogenically different conditions such as dysfunctional breathing or vocal cord dysfunction.<sup>96</sup> Thus, the potential for misclassification is considerable.

**The measurement of lung function in primary care is difficult**

Tests of variable airflow restriction are difficult to do in non-specialist settings where most cases of asthma are diagnosed, but also in children aged younger than 5 years in any clinical context. The assessment of airway responsiveness is also difficult, which is unfortunate because tests of airway responsiveness are sufficiently sensitive that a negative result provides strong evidence against a diagnosis of asthma. As a result of the relative difficulty of pulmonary function tests in the primary care setting and the absence of tests that rule out asthma as a diagnosis, primary care clinicians feel they have few options other than a trial-of-treatment approach with inhaled corticosteroids. This approach is flawed because conditions that mimic asthma (which often do not respond to corticosteroids) cause variable symptoms and might therefore improve spontaneously over time, leading to the mistaken belief that treatment with inhaled corticosteroids has been beneficial. The correct diagnosis is thus delayed, or inappropriate treatment might be increased when symptoms worsen. It is also not necessarily valid to draw inferences about the longer-term benefits of treatment (ie, reduction in frequency of asthma attacks) from the outcome of a short-term trial. Moreover, expectation, observer and ascertainment biases, and incomplete adherence to the prescribed treatment can complicate interpretation of the trial. Most of these problems, in addition to the inclination of clinicians to be cautious in borderline cases, increase the likelihood that patients might be started on inappropriate inhaled corticosteroid therapy, with associated cost and potential toxicity. Increasing evidence suggests that overtreatment is common: observational studies show that 60% of patients referred to secondary care<sup>97</sup> and 30% of patients in primary care<sup>98</sup> have no objective evidence of airway dysfunction or inflammation and do not deteriorate when inhaled corticosteroid treatment is stepped down. One consequence of inhalers being used so liberally is that the diagnosis of asthma has become trivialised. This trivialisation might be one of the reasons why promoting the importance of long-term treatment to an increasingly sceptical population is difficult.

**Current diagnostic approaches for asthma do a poor job of identifying patients who are at high risk for serious outcomes**

This problem is evidenced by data from national enquiries<sup>86</sup> into asthma deaths showing that patients with asthma that is perceived to be mild and low risk continue to die of the disease. Strategies are needed that identify high-risk disease more clearly, and engage patients in ways that encourage them to adhere to their treatment. The current treatment-based definitions of severe asthma need to be modified to encompass elements of physician and patient behaviour.

**The use of umbrella diagnostic terms has disadvantages**

Conventional wisdom indicates that asthma and chronic obstructive pulmonary disease (COPD) are distinct, and guidelines recommend different management approaches,<sup>36,37,99</sup> particularly regarding the use of inhaled corticosteroids. The reality is that the diseases overlap substantially, with cross-sectional studies showing mixed physiological, radiological, and pathological features in patients with a diagnosis of one or the other and community studies showing that many patients have mixed features.<sup>100</sup> The response of the clinical community to this overlap has been to invent another umbrella term: asthma COPD overlap syndrome.<sup>101</sup> This term has the demerits of combining two problematic umbrella terms to make a third one that is even more problematic.<sup>102</sup> Asthma COPD overlap syndrome can be characterised by a COPD-like systemic inflammatory profile; asthma COPD overlap syndrome, asthma, and COPD might be neutrophilic, eosinophilic or mixed; and bronchodilator reversibility fails to distinguish anything from anything else.<sup>103</sup> Crucially, the clinical relevance of individual features, such as eosinophilic airway inflammation and fixed airflow limitation, and their genetic associations, seem to be similar, if not identical, in asthma and COPD irrespective of the label.<sup>103,104</sup> Thus, the importance of using such labels becomes questionable and might even be counterproductive in view of the clear potential for misclassification and inappropriate use of inhaled corticosteroids and long-acting  $\beta_2$ -agonist monotherapy.

**Few treatments exist for poorly characterised airway diseases**

Failure to look beyond current diagnostic labels prevents the exploration of causes of morbidity in patients who have chronic cough or wheezing associated with viral respiratory tract infections. These airway diseases have a relatively distinct clinical phenotype, but are not easily placed in the classification system for asthma or COPD. Thus, the mechanisms of these common conditions are only understood superficially, and no specific treatment approaches are available. Many patients sit uneasily under the asthma umbrella and receive regular asthma treatment with little evidence of benefit. Failure to clearly identify and study these specific patient populations results in almost no interest from the pharmaceutical industry, and thus few prospects for effective treatments.

(Continues on next page)

(Panel 4 continued from previous page)

**Incorrect assumption that a causal link exists between variable airflow obstruction and eosinophilic airway inflammation**

The identification of variable airflow obstruction in the definition and diagnostic process for asthma might explain why this pattern of airway dysfunction is widely assumed to indicate a discrete airway pathology (eosinophilic airway inflammation). This assumption is now known to be incorrect.<sup>28</sup> Severe eosinophilic airway inflammation might even be associated with loss of bronchodilator reversibility<sup>105</sup> and 40–50% of patients with objective evidence of variable airflow obstruction have non-eosinophilic pathology (or no detectable airway inflammation).<sup>106</sup> Thus, although the demonstration of variable airflow obstruction might be a reasonable basis on which to start bronchodilator therapy, it cannot be used to identify patients likely to respond to steroids or more specific inhibitors of eosinophilic airway inflammation.

**The disparity between defining characteristics of asthma and important outcomes (risk of attacks, likelihood of a response to corticosteroid treatment) might represent another reason why clinicians commonly adopt a no-test approach to diagnosis**

However, rapid progress in the development of biomarkers of airway inflammation has been observed. For example, several reliable markers of eosinophilic airway inflammation have been

identified, which provide a better perspective on risk of attacks<sup>107,108</sup> and the likely response to treatment with corticosteroids<sup>6,108,109</sup> than traditional physiological measures (table 1). Some of these biomarkers (eg, blood eosinophil count, fraction of exhaled nitric oxide [FeNO]) have the additional benefit of being easy to measure, making them ideal for use in non-specialist practice.<sup>6</sup> Increasing evidence<sup>6,27,108</sup> indicates that these biomarkers stratify risk effectively and result in more effective and economical use of existing and new treatments. The howls of rage from some members of the clinical community following the suggestion by the UK National Institute for Clinical Excellence that FeNO should have a place in the diagnosis of asthma are almost incomprehensible. Even in the 21st century, a diagnosis of asthma is frequently made, and long-term treatment initiated, without any objective diagnostic measurements ever being made. Would this approach be used for any other chronic disease for which objective diagnostic tests are readily available? Although the Commissioners differed in their views on the strength of evidence for diagnosis and management guided by biomarkers, particularly in children, we unanimously agreed that the inclusion of biomarkers in the diagnostic process could only enhance the capacity to diagnose asthma that is responsive to inhaled corticosteroids, resulting in a shift from the current approach that diagnoses the umbrella term asthma, towards the diagnosis of asthma phenotypes that respond to specific treatments.

	Association with treatment response	Invasiveness	Comments
FeNO	Corticosteroids, anti-interleukin 13, anti-interleukin 4 and anti-interleukin 13, anti-IgE	Non-invasive	Easy, quick, not specific, cheap, generally available; loses specificity in smokers <sup>110</sup>
Serum IgE	No association	Minimal	Although recommended, no clear association has been identified between IgE or allergy as a biomarker of treatment responses or clinical outcome <sup>111</sup>
Serum periostin	Anti-interleukin 13, anti-IgE	Minimal	Effect shown with anti-interleukin 13, poor availability; confounded by growth in childhood, pregnancy, and dental disease <sup>112</sup>
Blood eosinophil count	Oral corticosteroids, anti-interleukin 5	Minimal	Generally available, high clinical impact, predicts anti-interleukin 5 response <sup>12</sup> and response to inhaled corticosteroids in chronic obstructive pulmonary disease; <sup>108</sup> associated with increased risk of lung attacks <sup>107,108</sup>
Sputum eosinophil count	Corticosteroids, anti-interleukin 5	Moderate	Available at specialist centres, tissue specific, time-consuming; good therapeutic marker for inhaled corticosteroids, oral corticosteroids, and biological drugs; established evidence of value as a monitoring tool

FeNO=fraction of exhaled nitric oxide.

**Table 1: Potential biomarkers of eosinophilic airway inflammation**

management, but this abnormality cannot be modified until clinicians can distinguish between the airflow limitation that is due to an active, treatable factor, and that which is irreversibly programmed in early life or prenatally.

**Diagnostic and monitoring approaches**

Despite the variable manifestations of asthma discussed previously, the main approach to diagnosis has been to document asthma symptoms and variable airflow

limitation, an approach which has changed little in 50 years. Reliance on measures of airflow limitation is problematic for seven reasons (panel 4).

**New drug development**

Until 2014, the developments in new drug discovery enjoyed by other specialty areas had not been seen with asthma (table 2).<sup>21</sup> The slow progress in this area perhaps highlights the limitations of our existing view of asthma and airway disease most obviously. New asthma treatments

are largely variants on the old; a brownie inhaler, with more potent topical effects, despite increasing concerns about topical immunosuppression.<sup>113</sup> When new treatments become available, they are widely prescribed to all patients despite being largely ineffective (eg, sodium cromoglicate and ketotifen fumarate) or effective only in subgroups of patients (eg, omalizumab and mepolizumab). Until recently, the concept of targeted treatment did not exist. Progress in new drug discovery has been slow, with relatively few molecules progressing from the laboratory to the clinic and a depressingly high rate of failure at the later stages of clinical development (table 2).<sup>21</sup>

Mepolizumab, a humanised monoclonal antibody that was developed to inhibit eosinophilic airway inflammation by blocking interleukin 5, is a good example of stalled progress in new drug discovery. Mepolizumab was found to be safe and effective at blocking interleukin 5 and reducing eosinophilic airway inflammation when tested using in-vitro systems and in-vivo models.<sup>114,115</sup> A subsequent clinical trial<sup>116</sup> was designed that incorporated mepolizumab into a step-up guideline-based framework. Within this framework, mepolizumab was investigated in patients who remained symptomatic on current inhaled corticosteroid therapy and the clinical trial focused on lung function and asthma symptoms as traditional outcome measures. Despite adequate power, the results of this trial were unexpectedly negative, which led to the near-abandonment of the drug.<sup>117</sup>

Investigators who were experienced with non-invasive measures of airway inflammation identified two important problems with this initial clinical trial: the heterogeneity of airway inflammation in severe asthma meant that a considerable number of the trial participants would not have had eosinophilic airway inflammation and therefore would not be expected to respond; and the occurrence of asthma attacks is closely linked to eosinophilic airway inflammation<sup>113,28,117,118</sup> and might have been a better outcome measure than lung function and asthma symptoms. Two investigator-initiated studies<sup>28,118</sup> were designed to target mepolizumab specifically to patients with severe asthma and sputum eosinophilia, using asthma attacks as an outcome. In both studies, mepolizumab treatment was associated with decreased asthma attacks with effect sizes of 50–80% (figure 4).<sup>119</sup> Subsequent phase 2b<sup>12</sup> and 3<sup>120,121</sup> trials confirmed these findings and, with refinements in the criteria used to identify the treatment target, were able to show a wider range of clinical benefits closely linked to a raised blood eosinophil count. Measures of variable airflow limitation and symptoms, previously regarded as defining characteristics of asthma, were of no value in predicting treatment response,<sup>12,105</sup> nor seemingly was the label of asthma because robust treatment responses were seen in patients with features of COPD with evidence of eosinophilic airway inflammation.<sup>12</sup> The same general principle has been instrumental in the development of a range of biological drugs that target interleukin 5,<sup>122,123</sup>

	Drugs (n)	Market entry probability (%)	Cumulative market entry probability (%)
HIV and AIDS	108	Phase 2 trials 75%; phase 3 trials 50%; approved 39%	14%
Dermatology	122	Phase 2 trials 8%; phase 3 trials 44%; approved 29%	11%
Haematology	163	Phase 2 trials 60%; phase 3 trials 4%; approved 22%	9%
Neurology	192	Phase 2 trials 73%; phase 3 trials 47%; approved 22%	8%
Cancer	68	Phase 2 trials 78%; phase 3 trials 46%; approved 20%	7%
Cardiovascular	280	Phase 2 trials 69%; phase 3 trials 4%; approved 22%	6%
Respiratory	165	Phase 2 trials 68%; phase 3 trials 31%; approved 16%	3%

Figures represent percentage of drugs unless otherwise indicated.

Table 2: New drug discovery in different fields of medicine<sup>21</sup>

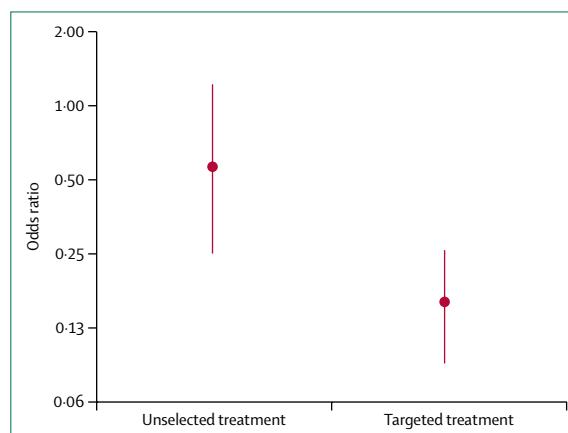


Figure 4: Comparative effect sizes for exacerbation rates following treatment with 250 mg intravenous mepolizumab, using control-based (unselected) and targeted therapy-based (selected) treatment models in patients with severe eosinophilic asthma<sup>119</sup>

Considerable benefit in an important subgroup is missed if all patients are treated unselectively. Bars indicate 95% confidence intervals.

interleukin-13,<sup>30,31</sup> and interleukin-4 and interleukin-13<sup>29</sup> pathways, many of which have shown signs of efficacy in late phase clinical trials (table 3).

### Where do we want to go?

The Commissioners believe that what is needed is a third era of asthma management, which accounts for the increasingly recognised heterogeneity of asthma and offers precision management and targeted treatment on the basis of careful assessment of the characteristics of a patient's disease. This third era will be particularly important if we are to take advantage of the many drugs in development that inhibit type 2 inflammation. Other pathogenically important and tractable mechanisms also need to be identified.

One important question is whether the phenotypic heterogeneity of asthma can be explained by discrete mechanistic pathways or endotypes.<sup>125</sup> For example, the systemic inflammation associated with obesity and old age might have effects in the airways that worsen asthma.<sup>126</sup> This is a complex area because there is a limit to how much phenotypic heterogeneity can inform our

understanding of endotypes because many phenotypic traits (ie, symptoms, airflow obstruction) can be caused by multiple disease mechanisms<sup>125,127</sup>—eg, many kidney diseases cause uraemia. For this reason, a reductionist approach, which focuses on traits that are recognisable, linked to morbidity, and associated with treatment response might represent a better conceptual framework to accelerate progress towards personalised treatments.<sup>127–130</sup> In the short-term, research should focus on these treatable traits, while searching for mechanistic underpinning of different disease traits. The important principle is that ultimately, mechanisms will drive the precision.

### Treatable traits

Any biological tube reacts to stimuli with a small and stereotypic set of responses, irrespective of the underlying stimulus. This is hardly a revolutionary concept: irrespective of how the kidney is damaged, the failing organ cannot excrete creatinine, and blood levels rise. On the basis of the ideas of Hargreave,<sup>131</sup> and with the introduction of several new traits, the stereotypic responses of the airway to adverse events are (in order of importance and recognisability) any or all of the following: airflow limitation, airway inflammation, airway infection and impaired airway defences, and altered cough reflex sensitivity and efficacy.

### Airflow limitation

Airflow limitation represents a treatable trait if due to repeated contraction of airway smooth muscle and perhaps inflammatory oedema (mural) of the airway wall and intraluminal factors (airway secretions). However, variable airflow limitation might be due to less treatable problems such as loss of so-called alveolar guy ropes (extramural). Wheeze is not always a result of airway smooth muscle contraction, and the cause of wheeze and response to treatment needs to be understood. Furthermore, paediatrics challenges the conventional view of airway hyper-responsiveness; just as multiple atopies exist, multiple forms of hyper-responsiveness exist. Three prospective birth cohort studies<sup>68–70</sup> have shown that airway hyper-responsiveness is present within weeks of birth, at a time when no evidence of allergy, airway inflammation, or increased airway smooth muscle mast cell infiltration,<sup>132</sup> exists and is strongly predictive of medium term respiratory outcomes. Animal and a small amount of human data<sup>133</sup> suggest the underlying cause is a change in airway dimensions (elongation and narrowing) and loss of airway tethering points, such that any narrowing of the airway leads to an exaggerated obstructive signal. Subsequently, multiple additional and potentially more treatable factors are likely to contribute to airflow limitation, including sensitisation of airway nerves, mast cells, and smooth

Patient selection criteria	Forced expiratory volume	Airway hyper-responsiveness	Asthma control questionnaire score	Exacerbations	Oral corticosteroid-sparing effect	Quality of life questionnaire	Blood eosinophil count	Sputum eosinophil count	FeNO	Serum IgE	Comments	
Anti-interleukin 5	Blood and sputum eosinophil count and exacerbation rate	+	0	+	++	++	++	↓↓	↓	0	0	Clinical effects in specific subgroup of severe asthma
Anti-IgE	Blood IgE, positive allergen-specific IgE, IgE concentration, positive skin prick test, FeNO*, blood eosinophils*	+	0	+	++	Unclear	+	↓	↓	↓↓	0	Most randomised controlled trials focused on moderate to severe asthma, less evidence in very severe asthma
Anti-interleukin 13	Periostin concentration, FeNO	+	Unclear	+	+	NA	0	↑	Unclear	↓↓	↓	Partially based on subgroup analysis
Anti-interleukin 4 and anti-interleukin 13	Periostin, FeNO, and blood eosinophils	++	Unclear	++	++	Unclear	NA	↑	Unclear	↓↓	↓↓	Promising approach potentially offering more efficacy than achieved with single cytokine blockade <sup>124</sup>

FeNO=fraction of exhaled nitric oxide. + =modest clinical improvement. ++=large clinical improvement. 0=measured and no effect observed. ↓↓=large decrease. ↓=modest decrease. Unclear=measured but not enough datapoints for a conclusion. NA=not applicable. ↑=modest increase. \*Not yet used for patient selection but shown to be highly predictive of a response.<sup>12,28</sup>

Table 3: Effect of type 2 cytokine-associated monoclonal antibodies on clinical endpoints and biomarkers used for patient selection in severe eosinophilic asthma

muscle by inflammatory mediators,<sup>134</sup> reduced epithelial barrier function, reduced production of bronchoprotective factors,<sup>135</sup> an intrinsic abnormality of airway smooth muscle,<sup>136</sup> and some structural changes to the airway.<sup>134</sup>

Airflow limitation might be unresponsive to bronchodilators and anti-inflammatory treatment. Although fixed airflow limitation might not represent a treatable trait, it is certainly a trait that can lead to overtreatment if not considered correctly. Early-life factors might be the most important cause of the structural changes that occur in the airway leading to fixed airflow limitation.<sup>55,137–139</sup> The birth cohort studies<sup>68–70</sup> show that structural changes in the airways first develop antenatally and in early childhood, and studies<sup>140</sup> in adults show that, although a subset of patients have rapid deterioration in spirometry, many people with or without asthma or COPD, have normal lung ageing. Early lung function loss might be associated with circumferential narrowing or elongation of the airway itself, which might be developmentally determined in utero,<sup>141</sup> or postnatally, in association with viral infection (obliterative bronchiolitis)<sup>142,143</sup> and pollution<sup>144</sup> or loss of the alveolar guy rope attachments. Animal data suggest that these so-called guy rope attachments are reduced by antenatal smoke exposure.<sup>145</sup> Airflow limitation has been observed soon after birth—eg, in infants of mothers who smoked during pregnancy<sup>146</sup>—long before airway inflammation is evident.<sup>79,147</sup> The consequences of pre-term birth and early-life bronchopulmonary dysplasia are another increasingly recognised cause of fixed airflow limitation in later life.<sup>148</sup>

The considerable number of patients with asthma who have fixed airflow limitation highlights the potential for clinically important misclassification if umbrella terms continue to be used. This problem would disappear if practice moved towards a more precise and clinically useful approach that uses only the term chronic airway disease (similar to anaemia as discussed previously) and describes the particular treatable traits present in a particular individual. The identification of fixed airflow limitation might be difficult in an individual, and in children in particular, because no agreed definition of an adequate treatment trial exists for this purpose. Sometimes airflow limitation is apparently fixed but responds well to anti-inflammatory treatment, presumably as a result of improvement in airway oedema or mucus plugging. However, the possibility that airflow limitation is fixed and due to poor lung development or irreversible structural changes should always be considered before escalating treatment when evidence of airway inflammation is absent.

New imaging techniques and more sensitive physiological measures might provide new and clinically important information about mechanisms leading to fixed and variable limitation, but until this information is obtained the underlying causes of airflow limitation cannot always be attributed to discrete treatable traits. The goal should be to identify largely fixed airflow

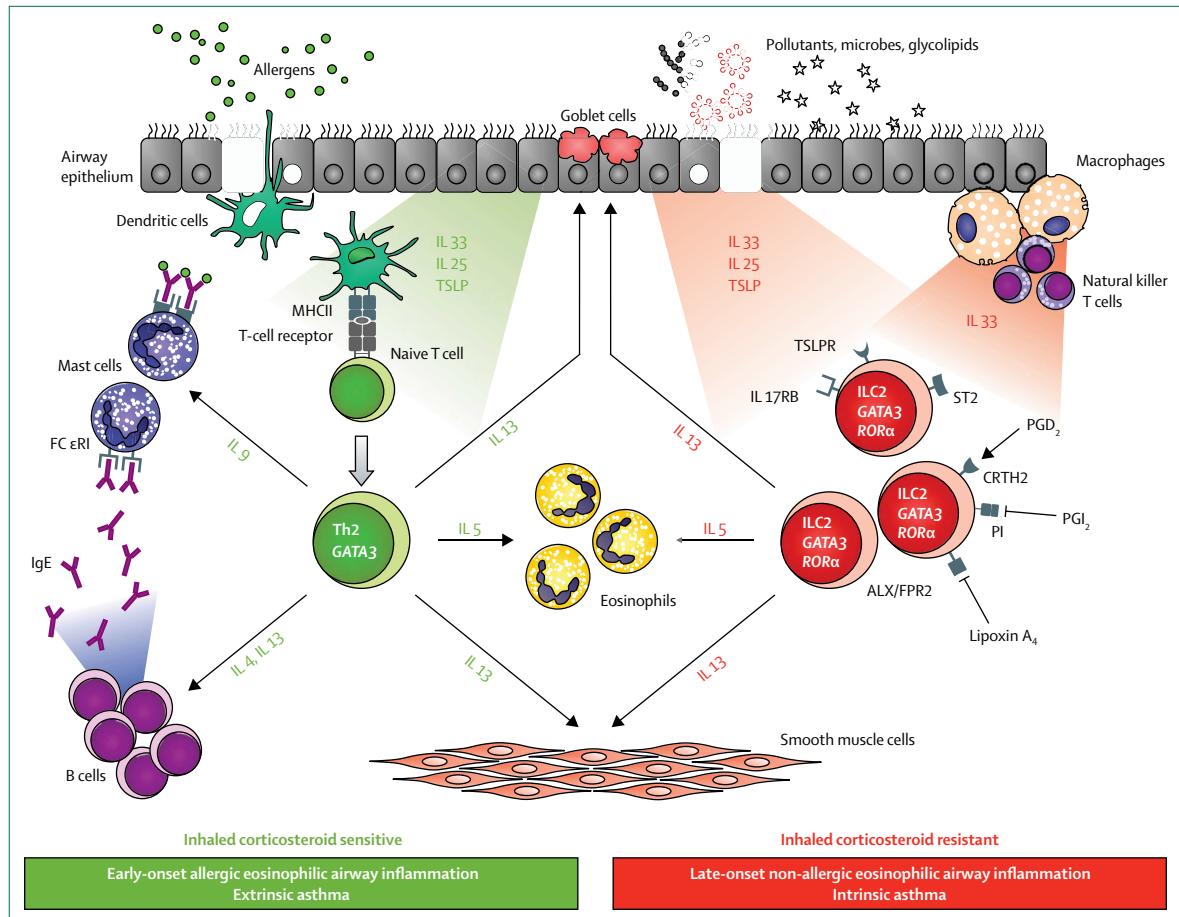
limitation and suspected episodic airflow limitation and to use measures of airflow limitation to define best achievable function in response to treatment. Repeated assessments over time might be necessary to achieve this.

#### Airway inflammation

Airway inflammation is heterogeneous among patients with a label of asthma. Eosinophilic airway inflammation is an important pattern because it is recognisable (table 1) and treatable. In patients with eosinophilic asthma, two different pathogenic pathways are thought to lead to eosinophilic airway inflammation, differing in their link to allergy, in their master regulator lymphocyte population, and probably also in their responsiveness to treatment with inhaled corticosteroids (figure 5).<sup>149</sup> Other pathways might exist, hitherto undiscovered. The exact mechanisms and the clinical implications of these different pathways remain to be defined but they could theoretically represent individual and distinct treatable traits. In view of the proliferation of high-cost monoclonal drugs, we need to understand pathways in the individual patient rather than proceed with a haphazard series of n-of-1 therapeutic trials.

Prospects for identifying and modifying airway inflammation in type 2-low disease are much more uncertain.<sup>150,151</sup> We have therefore not included this as an individual treatable trait. The beneficial effects of long-term treatment with low-dose macrolides in patients with non-eosinophilic asthma<sup>152,153</sup> suggest that airway inflammation in type-2 low disease might represent an individual treatable trait, but CXCR2 antagonists, which cause a marked reduction in sputum neutrophil counts,<sup>154</sup> have no efficacy in patients with uncontrolled asthma.<sup>155</sup> In patients with COPD, macrolides and CXCR2 antagonists have very different effects in smokers and ex-smokers; CXCR2 antagonists effectively reduce exacerbations in smokers but not ex-smokers<sup>156</sup> whereas macrolides have the opposite effect.<sup>157</sup> These findings suggest that at least two types of neutrophilic airway inflammation exist in patients with airway disease, differing in their relationship with smoking and airway infection. Indeed, neutrophilic inflammation might be beneficial<sup>158</sup> in the presence of bacterial airway infection (which is increasingly implicated in asthma), as shown by a 2014 cystic fibrosis trial<sup>159</sup> of an anti-leukotriene B<sub>4</sub> strategy. This trial showed that the mere presence of inflammation is not a sufficient reason to eradicate it.

Neutrophilic airway inflammation might also be driven by T-helper-17 cell-mediated processes. In the first clinical trial<sup>160</sup> of brodalumab, which blocks interleukin-17 signalling by inhibiting the interleukin-17 A receptor, the drug did not improve scores on an asthma control questionnaire (primary endpoint) in a group of patients with moderate to severe asthma. Treatment did have beneficial effects in a subgroup with high reversibility to salbutamol although this finding was not confirmed in a subsequent phase 3 trial (unpublished). A selective beneficial effect in bronchodilator responsive



**Figure 5: Pathways leading to eosinophilic airway inflammation**

Modified from Bruselle et al.<sup>149</sup> ALX/FPR2=G-protein coupled formyl peptide receptor 2. CTRH2=prostaglandin D2 receptor 2. IL=interleukin. ILC2=type 2 innate lymphoid cell. MHCII=major histocompatibility complex II. PI=phosphoinositide. PGD<sub>2</sub>=prostaglandin D2. PGI<sub>2</sub>=prostacyclin I2. ST2=interleukin 1 receptor-like 1. Th2=T-helper-2 cell. TSLP=thymic stromal lymphopoietin. TSLPR=thymic stromal lymphopoietin receptor.

patients with severe asthma has also been reported with the tumour necrosis factor- $\alpha$  antagonist golimumab, although this treatment was not pursued because the treated population had a high incidence of malignancy.<sup>161</sup> Patient selection was not optimum in either the golimumab or brodalumab study because the presence of neutrophilic airway inflammation was not confirmed and markers of tumour necrosis factor- $\alpha$ <sup>162</sup> or interleukin-17 involvement were not included as criteria for patient selection. However, a definable subgroup of patients with severe asthma who derive net benefit from one or both of these treatments might exist.

#### Airway infection and impaired airway defences

Little doubt exists that viral infections are an important trigger for acute severe asthma attacks and growing evidence suggests that an abnormal airway response to infectious respiratory viruses results in an amplified airway inflammatory response and serious clinical consequences such as asthma attacks.<sup>163,164</sup> Challengingly, bacterial infection and viral infection have been shown to

be present in acute asthma attacks.<sup>165</sup> Both types of infection are potentially identifiable and are therefore candidate treatable traits in patients with asthma and existing evidence suggests that inhaled interferon  $\gamma$  has efficacy in patients with severe asthma.<sup>95</sup> However, before antibiotic therapy is recommended for the treatment of attacks, transient, viral-induced, topical immunosuppression should be considered as an equally plausible reason for the presence of positive bacterial cultures.

#### Altered cough reflex sensitivity and efficacy

Cough is clearly an important airway defence mechanism, and the best treatment is to remove the underlying cause. Considerable age-associated changes occur in the diagnostic spectrum of isolated chronic cough. Cough reflex hypersensitivity is a common cause of symptoms in adult patients with a label of asthma, many of whom receive high intensity treatment with little or no evidence of benefit,<sup>166</sup> however, little is known about the extent to which this is a factor in children. Adult patients are usually women aged between 45 and 60 years who present

with a persistent dry cough associated with a heightened cough reflex, often in the absence of other features of airway disease.<sup>166</sup> Only a small proportion of patients have cough reflex hypersensitivity secondary to treatable eosinophilic airway inflammation.<sup>167</sup> Other treatable causes include cough secondary to angiotensin converting enzyme inhibitor treatment; however, a considerable proportion of patients have an altered cough reflex with no obvious cause.<sup>166</sup> This component of airway disease is recognisable and quantifiable,<sup>166</sup> and thus represents an important area for new research and for new drug development with encouraging signs of progress.<sup>168</sup> Similarly, reduced sensitivity or effectiveness of the cough reflex, associated with medication or neuromuscular disease respectively, could theoretically be treated with cough augmentation techniques.

#### *Treatable traits and the classification of airways diseases*

We acknowledge that determining all the factors of airway disease in every patient, especially children, might not be possible, but the potential complexities should at least be considered. Spirometry is difficult for young children to perform and might not be sensitive enough to detect important abnormalities in some patients,<sup>169</sup> but other reliable lung function techniques exist that are less dependent on cooperation by toddlers and infants and might be more sensitive.<sup>170,171</sup> Lower airway inflammation can only be assessed in severe cases as bronchoscopy is not justified in most children with asthma. Measurements in nasal secretions and breath analysis are accessible, and future research should focus on finding clinically relevant measures or genetic markers so that airway disease can be deconstructed in a 21st century way. These measures are obviously not applicable in patients with mild airway disease in whom there is little diagnostic doubt, for example in primary care in particular, adults or children with an airway disease that is completely responsive to low-dose inhaled corticosteroids will clearly not want to submit to multiple airway tests. These traits are not separate discrete entities—eg, chronic airway bacterial infection might lead to neutrophilic inflammation and increased airway secretory products. The treatable manifestations of airway disease must be considered, without neglecting the need to develop novel therapies for intractable issues. Some or all of these traits could have long-term implications that specifically confer future risk despite no apparent immediate harm, which could have important implications.

#### **Precision management**

Richard Asher<sup>172</sup> stated that as a clinical community we still confuse clinical observations and pathology, and name entities in a confusing way, which leads to muddled concepts of disease. Our use of the term asthma is a prime example of this, whereby guidelines have conflated symptoms (cough, wheeze, and breathlessness), physiology (variable airflow limitation), and pathology (eosinophilic airway inflammation). Therefore, clinicians

must describe what they see, using the framework shown in table 4 as at least a starting basis, acknowledge knowledge gaps, and use terminology to illuminate not obscure. Consequently, asthma becomes a syndrome, and a diagnosis for a specific individual should now become an airway disease or asthma syndrome characterised by fixed and variable airflow obstruction, without eosinophilic airway inflammation or chronic infection, whereby high-dose inhaled corticosteroids will not be prescribed and future risk will be quantified and modified where possible.

Until precision management is available, the traits of the asthma syndrome discussed previously and in table 4 can be used. These traits have the merits of being linked to morbidity, and some are reasonably well defined, measurable, and linked to specific treatment responses. We recommend these traits are used to structure an alternative approach to assessment and management, similar to that described by Agusti and colleagues.<sup>129</sup>

The first generic question when a physician assesses a patient of any age is: are any comorbidities or lifestyle factors present that might be contributing to the clinical problem? Identification and modification of these traits (tables 5, 6) is likely to be helpful irrespective of whether the patient has underlying airway disease. The second question is: which aspects of the patient's problems are due to airway disease? Assessment of the clinical history, the presence of risk factors of airway diseases (eg, smoking, allergies, occupation, family history, and respiratory disease in early life), spirometry, and readily accessible biomarkers of type 2 inflammation should help to answer this key question. If a high probability of airway disease is suspected, the next step is to establish which traits are driving airway disease in this particular patient and treat them accordingly, with consideration of the likely outcomes of that treatment (table 4). In patients in whom airways disease seems unlikely, is refractory to simple treatments, or morbidity is disproportionate to what has been demonstrated objectively, attention should again turn to environmental or extrapulmonary factors that might be relevant and modifiable (tables 5, 6).

This strategy recognises the clinical and biological complexity of airway disease and acknowledges that both clinical phenotypes and endotypes can occur in isolation or in combination in any patient and might change over time, either as part of the natural history of the disease or because of therapy. Importantly no causal link should be assumed to exist between one component and another. The strategy encompasses overlapping disorders, comorbidities, environmental and lifestyle factors, and emphasises the consideration of these in patients with persisting morbidity despite effective intervention against pulmonary treatable traits.

The components listed in tables 4–6 should be viewed as a first step towards a new diagnostic and management

		Likely effect of treatment*			Factors associated with better treatment response	Comments
	Recognition	Treatments	Patient-related outcomes	Surrogate outcomes		
Airflow limitation†	FEV <sub>1</sub> /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 (ie, mucosal oedema, mucus plugging) Loss of airway support probable if imaging or physiological evidence of emphysema	β <sub>2</sub> -agonists (short-acting and long-acting) Antimuscarinic agents (ie, long-acting) Theophylline Bronchial thermoplasty might have benefit Loss of airway support might respond to lung volume reduction strategies	Decreased symptom scores Improved QoL Small reduction in attacks (particularly less severe) Increased exercise capacity	Improved FEV <sub>1</sub> Improved PEF Reduced airway responsiveness	Acute bronchodilator response Airway hyper-responsiveness Eosinophilic airway inflammation	Different classes of bronchodilators have additive effects Bronchodilator therapy increases probability of patients discontinuing ICS; <sup>90</sup> do not use in separate inhalers in patients with eosinophilic airway inflammation or those who might have variable symptoms and inflammation Underlying causes of airflow limitation will not be definable in many patients Goal should be to identify largely fixed airflow limitation and suspected episodic airflow limitation and to use measures of airflow limitation to define best achievable function
Eosinophilic airway inflammation	See table 1	ICS and OCS See table 3	See table 3	See table 3	See tables 1, 3	Different biomarkers provide complimentary information <sup>107</sup> Suspect episodic inflammation in patients with episodic symptoms Some patients have ICS-resistant disease and require systemic therapy Severe eosinophilic airway inflammation can be associated with aspirin-sensitivity and nasal polyps
Infection	Sputum culture Sputum PCR	Antibiotics (ie, long-term low-dose macrolides) Inhaled interferon β (viral infection) Influenza vaccination Antifungal drugs (only effective in patients sensitised to aspergillus and colonised)	Reduced attacks Decreased symptom scores Improved QoL	Small improvement in FEV <sub>1</sub> Negative culture Reduced qPCR Reduced sputum neutrophils	Focal chest signs Sputum production Fever; viral URTI Positive culture High sputum qPCR Neutrophilic airway inflammation	Macrolide effect suspected to be associated with bacterial infection Viral infection are major cause of attacks Role of fungal infection and hypersensitivity unclear Interaction between different microorganisms and with host poorly understood
Cough reflex hypersensitivity	Increased cough reflex sensitivity (ie, capsaicin) Increased cough counts Cough symptom scores	Speech therapy P2X3 antagonist Gabapentin ICS and OCS Stop treatment with ACE inhibitor	Decreased symptom scores Improved QoL Cough frequency	Cough sensitivity	Eosinophilic airway inflammation (ICS, OCS) Use of ACE inhibitor Presence of comorbid factor (smoking particularly)	Important but poorly understood cause of morbidity Mainly occurs in women aged between 45 and 55 years Sometimes due to environmental and behavioural factors

ACE=angiotensin converting enzyme. ASM=airway smooth muscle. FEV<sub>1</sub>=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroid. LABA=long-acting β<sub>2</sub> agonist. LAMA=long-acting antimuscarinic. LLN=lower limit of normal. OCS=oral corticosteroid. PEF=peak expiratory flow. SABA=short-acting β<sub>2</sub> agonist. QoL=quality of life. URTI=upper respiratory tract infection.\*Patient effects were classified as patient-related outcomes (ie, of direct relevance to patients) or surrogate outcomes (ie, indirect measures). † Airflow limitation could be due to multiple factors including variable factors (ie, airway smooth muscle contraction, mucosal oedema, and mucus plugging) or more fixed factors (ie, airway fibrosis, loss of airway support from elastic recoil), but at present few methods are available to distinguish these individual components.

Table 4: Pulmonary treatable traits of airways diseases

approach and we would hope that they are refined and more specifically targeted to more clinically important mechanisms with time. With the advent of an increasing number of monoclonal drugs, we need to move beyond cell-based definitions to pathway-based definitions, particularly in non-eosinophilic airway diseases. Although not definitive, consistent evidence suggests that the type of individualised multidimensional

management plan we advocate leads to reduction in the frequency of attacks, improved quality of life, and more economical use of treatment.<sup>10,11,26,27,174,175</sup> Additional strengths of this proposal are:<sup>129</sup>

- Specific diagnostic criteria for the components are proposed, and expected treatment benefits outlined, in terms of patient relevant and surrogate outcome measures (tables 4–6)

	Identification	Treatments	Likely effect of intervention*		Factors associated with better treatment response	Comments
			Patient-related outcomes	Surrogate outcomes		
Rhinitis, gastro-oesophageal reflux	Suggestive symptoms Imaging Oesophageal manometry	Nasal steroids, proton-pump inhibitors	Decreased symptom scores, improved quality of life	Improved imaging appearances, nasal inspiratory flow, oesophageal manometry	Chronic rhinosinusitis with polyps can be difficult to control with nasal steroids	Causes of asthma-like symptoms but direct link with lower airway disease unlikely
Obesity, deconditioning	Body-mass index Cardiorespiratory exercise test	Weight loss, bariatric surgery, rehabilitation or exercise training	Decreased symptom scores, improved quality of life, decreased cough frequency	Reduced body-mass index, improved 6 min walk test	Absence of comorbidity, good social support, group participation	Bariatric surgery most effective intervention for obesity, link with lower airway disease poorly understood
Anxiety, dysfunctional breathing, or vocal cord dysfunction	Disproportionate breathlessness Air hunger Frequent sighs Dizziness Light headed Tingling hands and face Chest tightness Increased Nijmegen questionnaire score <sup>973</sup> Noisy inspiration	Physiotherapy, breathing pattern retraining, counselling, speech therapy	Patient-related outcomes: decreased symptom scores, improved quality of life	..	Early recognition	Important but poorly understood causes of morbidity
Depression	Hospital anxiety and depression scale	Antidepressants	Decreased symptom scores	..	Might be associated with increased risk of death	Particularly important in severe disease
Treatment-associated morbidity	Angiotensin-converting enzyme inhibitor associated cough Breathlessness or tiredness secondary to β blocker	Withdraw or replace treatment	Decreased symptom scores, improved quality of life, decreased cough frequency	Reduced cough sensitivity, improved 6 min walk test	Angiotensin-converting enzyme inhibitor associated cough very likely to resolve on treatment withdrawal	Increasingly common
Other pulmonary or non-pulmonary condition	Focal chest signs Prominent crackles Clubbing Weight loss Haemoptysis Chest pain Cardiac history or risk factors Restrictive spirometry Abnormal chest x-ray or CT	Treatment of the underlying condition	Specific to underlying condition	Specific to underlying condition	Treatable condition	Cardiac disease commonly coexists and can be difficult to differentiate relative contributions

\*Patient effects were classified as patient-related outcomes (ie, of direct consequence to patients) or surrogate outcomes (ie, indirect measures).

Table 5: Comorbid factors potentially responsible for asthma-like symptoms

- This proposal recognises that different components are specifically associated with different aspects of the clinical problem or future risks (ie, eosinophilic airway inflammation and the risk of attacks)
- The proposal might be cost-effective because of more economical use of treatment and the expected larger therapeutic response
- The management plan can stimulate best translational research by identifying knowledge gaps
- Key inclusion and exclusion criteria can be identified for future randomised clinical trials
- The management plan can be applied in any patient with airway disease leading to more precise therapy, rather than label and one-size-fits-all approaches
- The plan can be used in any health-care setting by adapting the approach to the aspects of the condition that can be identified and modified in that setting

## Beyond guidelines: operationalisation of individualised treatment in different health-care settings

### Where are we now?

#### The rise and fall of guidelines

The framework for the management of asthma, recommended by numerous national and international guidelines, is a one-size-fits-all stepwise approach based on the level of asthma control (figure 6). This basic construct has not changed much since the first guidelines were published 27 years ago.<sup>14–17</sup> Current treatment is initiated with an inhaled short-acting β<sub>2</sub> agonists as required in intermittent asthma, with the addition of maintenance low-dose inhaled corticosteroids in mild persistent asthma, stepping up to combined inhaled corticosteroids or longacting β<sub>2</sub>-agonist therapy in moderate asthma, and an increased dose of inhaled

corticosteroids in the combination inhaler in severe asthma to obtain control. This control-based management approach results in treatment that is adjusted according to the same algorithm in all patients, through a continuous cycle of assessment, treatment, and review of the patient's response.

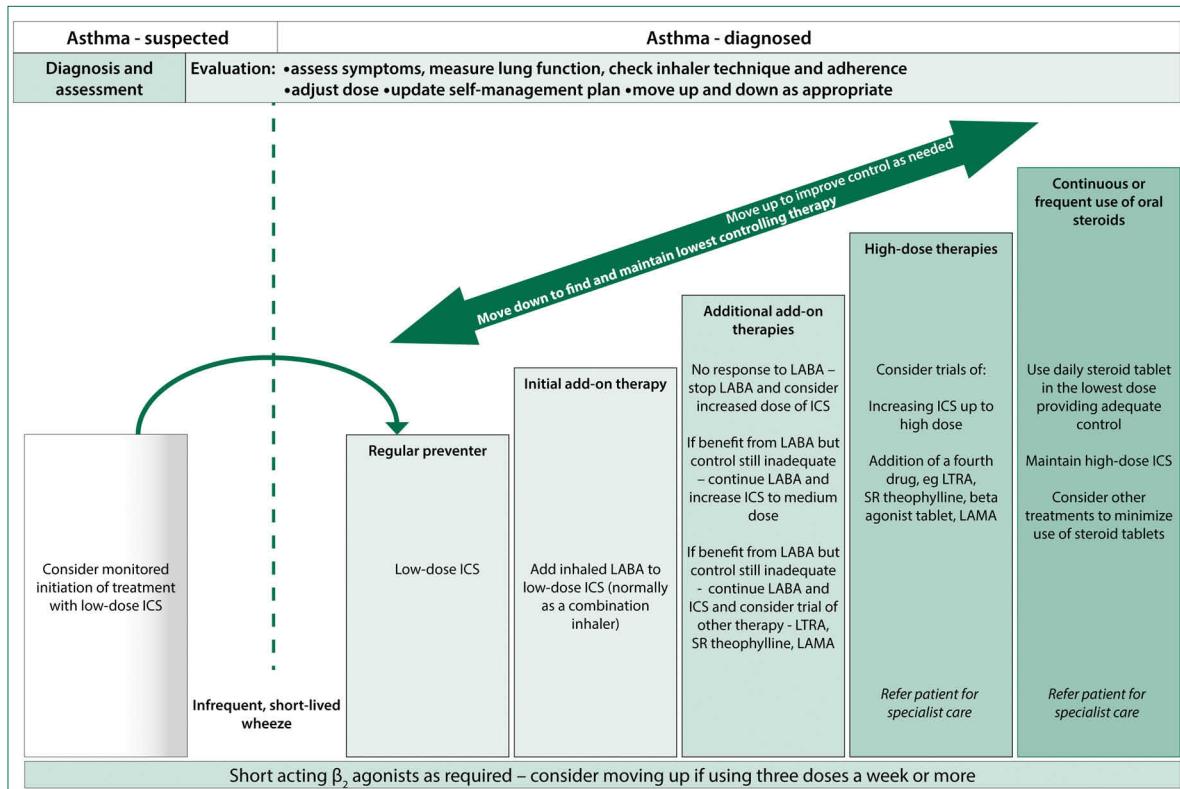
Guideline-based care works well when dealing with a homogeneous well defined condition, in which treatment responses are relatively consistent between patients and across different outcomes, and in patients for whom the goals of management are realistic and achievable; and indeed, for many patients, guidelines that recommend anti-inflammatory therapy have had substantial benefits. However, neither of the first two criteria are met in the whole spectrum of asthma. Perhaps guidelines were created without first establishing whether the entity whose management we are seeking to guide is useful and sufficiently well-defined.<sup>24</sup> An additional problem is that the goal of treatment—to eliminate symptoms and attacks and to normalise lung function—might be unachievable in a considerable proportion of patients.<sup>177,178</sup> Consequently, unachievable treatment goals drive treatment requirements (and cost) up in a spiralling manner.

The profusion, scope, and proliferation of modern guidelines have all led to problems. By necessity, guidelines result in recommendations that are conservative and formed on the basis of evidence from randomised controlled trials done in well-defined but poorly generalisable populations.<sup>179</sup> Treatment decisions at different steps are overgeneralised, resulting in illogical treatment in a considerable number of patients. For example, the addition of long-acting  $\beta_2$  agonists is recommended in patients whose condition is uncontrolled by low-dose inhaled corticosteroids, yet is this the best option for patients with evidence of active eosinophilic airway inflammation and whose predominant clinical problem is recurrent attacks? Patients who do not respond to the initial approaches (figure 6) need to be identified to enable the implementation of precision medicine rather than blindly following the standard step-up treatment plan. Early asthma guidelines discussed a few main concerns for diagnosing and treating the condition. However, subsequent guidelines have been lengthened, which has resulted in important recommendations being lost among minor self-evident ones. Increasingly, guidelines are used to establish medical and legal standards of care and thus, recommendations become set in stone, making it difficult

	Identification	Treatments	Likely effect of intervention*		Factors associated with better treatment response	Comments
			Patient-related outcomes	Surrogate outcomes		
Smoking and other environmental exposures	Smoking history Urinary cotinine Exhaled carbon dioxide	Cessation, treatment for nicotine addiction (nicotine replacement therapy, varenicline)	Decreased symptom scores, improved quality of life, reduction in number of attacks, increased exercise capacity, increased survival	Increased forced expiratory volume, increased peak expiratory flow, neutrophilic airway inflammation, reduced decline in lung function	Smoking history, addiction potential (perhaps genetic), presence of pre-existing lung disease	Difficult to modify, treatments for nicotine addiction doubles chances of sustained quitting, effect larger in early disease, associated with neutrophilic airway inflammation and a high potential for airway damage, important role in the induction of airway disease in prenatal and early life
Exposure to sensitiser (allergen, occupational)	Atopic tendency (presence of disease, family history) History (ie, latency) Relevant exposures Skin prick tests and radioallergosorbent tests	Avoidance, desensitisation, inhaled corticosteroids and oral corticosteroids, omalizumab, air filtration systems (uncertain)	Decreased symptom scores, improved quality of life, reduction in number of attacks, remission	Increased forced expiratory volume, increased peak expiratory flow, airway responsiveness, eosinophilic airway inflammation	Good evidence of sensitisation, monosensitisation, early recognition	Small evidence base, timing of intervention might be crucial, might be a secondary effect
Treatment adherence and device-associated factors	Prescription refill rates Drug concentrations Fraction of exhaled nitric oxide suppression test Chipped inhalers	Counselling and education, better inhalers, maintenance and reliever therapy with inhaled corticosteroids and short-acting $\beta$ agonists or inhaled corticosteroids and long-acting $\beta$ agonists, mobile and information technology reminders	Reduced number of attacks, decreased symptom scores, improved quality of life	Improvement in forced expiratory volume, reduced sputum eosinophils and fraction of exhaled nitric oxide	Poor inhaler technique more tractable than adherence issues	Common but difficult to detect and modify
Social and behavioural issues	Social history Home visit School and workplace information	Support	Decreased symptom scores, improved quality of life	..	..	Difficult to modify, particularly in adults

\*Patient effects were classified as patient-related outcomes (ie, of direct consequence to patients) or surrogate outcomes (ie, indirect measures).

Table 6: Important environmental and behavioural factors potentially associated with asthma-like symptoms



**Figure 6: British Thoracic Society and Scottish Intercollegiate Guidelines Network 2016 guideline for asthma management in adults**

Reproduced from the British Thoracic Society and Scottish Intercollegiate Guidelines Network Asthma Management Guideline 2016,<sup>176</sup> by permission of the Scottish Intercollegiate Guidelines Network. ICS=inhaled corticosteroid. LABA=long-acting  $\beta_2$  agonist. LAMA=long-acting antimuscarinic. LTRA=leukotriene receptor antagonist. SR=sustained release.

to innovate and generate new evidence. Furthermore, multiple guideline groups have emerged over the past 20 years leading, in some cases, to variable recommendations. Panel 5 summarises the conflicting views of three influential guidelines on the use of FeNO to guide diagnosis and management of asthma. The recommendations of these guidelines are contradictory because different questions were asked. The 2017 Global Initiative for Asthma<sup>37</sup> and the 2014 British Thoracic Society and Scottish Intercollegiate Guidelines Network<sup>181</sup> paediatric guideline groups asked: how valuable is FeNO in supporting a diagnosis of asthma? The groups concluded that it was not helpful. By contrast, the 2014 British Thoracic Society and Scottish Intercollegiate Guidelines Network<sup>181</sup> adult and 2011 American Thoracic Society Clinical Practice Guideline<sup>180</sup> groups came to a very different conclusion in response to a more specific question, which did not assume that asthma was a useful entity: which test best identifies eosinophilic airway inflammation and corticosteroid responsive airway disease?

#### Asthma management in low-income and middle-income countries

Poor precision of treatment and spiralling treatment costs are an important issue in low-income and middle-income

countries where tools required for diagnosis and effective inhaled therapies are routinely unavailable or unaffordable. Simple tests such as spirometry might have more utility in this setting as diagnostic overlap with respiratory infections or other chronic respiratory diseases occurs more commonly. Therefore, poor availability might be a factor leading to diagnostic error and potentially underdiagnosis. The implementation of so-called standard care is poor in high-income settings. The unacceptable inequity that still exists globally with regard to asthma diagnosis and management between low-income and high-income countries—whereby precision medicine and the need for individualised phenotyping to guide diagnosis and management is of priority in high-income settings, whereas even basic tools for diagnosis and management are not available in low-income settings—presents considerable challenges. Most of the childhood population worldwide and a substantial proportion of the worldwide adult population resides in low-income and middle-income countries, therefore addressing the challenges of diagnosis and management in these settings will have a considerable effect—eg, if inhaled beclometasone, inhaled salbutamol, prednisolone, and a milk bottle spacer were available to all, the global impact would be substantial.<sup>182</sup>

**Panel 5: Conflicting recommendations from guideline groups regarding the use of exhaled nitric oxide to diagnose and manage asthma**

**Global Initiative for Asthma 2017<sup>37</sup>**

Measurement of the fraction of exhaled nitric oxide (FeNO) is becoming more widely available. It is modestly associated with eosinophilic airway inflammation. FeNO has not been established as useful for ruling in or ruling out a diagnosis of asthma. FENO is high in eosinophilic asthma but also in non-asthma conditions (eg, eosinophilic bronchitis, atopy, allergic rhinitis, eczema), and is not elevated in some asthma phenotypes (eg, neutrophilic asthma). Several other factors affect FENO concentration: it is lower in smokers and is decreased during bronchoconstriction and in the early phases of allergic response, and might be increased or decreased during viral respiratory infections. In adult patients who are naïve to steroids (mainly non-smokers) with non-specific respiratory symptoms, FENO concentrations of more than 50 parts per billion were associated with a good short-term response to inhaled corticosteroids. However, no long-term studies have examined the safety of withholding inhaled corticosteroid treatment in patients with low initial FeNO concentrations. Consequently, in patients with a diagnosis or suspected diagnosis of asthma, FeNO cannot be recommended at present for deciding against treatment with inhaled corticosteroids.

**American Thoracic Society 2011 Clinical Practice Guideline<sup>180</sup>**

The use of FeNO is recommended for the diagnosis of eosinophilic airway inflammation. The use of FeNO is recommended to determine the likelihood of steroid responsiveness in patients with chronic respiratory symptoms possibly due to airway inflammation.

**British Thoracic Society and Scottish Intercollegiate Guidelines Network 2014 guidelines<sup>181</sup>**

**Paediatric patients**

The measurement of FeNO is feasible in unsedated children aged between 3 and 4 years. A raised FeNO concentration is neither a sensitive nor a specific marker of asthma with overlap with children without asthma. At present, insufficient evidence is available to recommend the use of markers of eosinophilic inflammation in the diagnosis of asthma in children. These markers might be useful for the assessment of disease severity or response to treatment.

**Adult patients**

An alternative and promising approach to the classification of airways disease is to use tests that best identify patients who will respond to corticosteroid therapy. A raised sputum eosinophil count and an increased FeNO concentration are more closely associated with corticosteroid response than other tests in a variety of clinical settings. Evidence also indicates that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment.

### Where do we want to go?

*From one-size-fits-all management to precision medicine*

New approaches are needed that deconstruct airway disease in all patients who do not respond to the initial treatment recommendation. The main limitation of the one-size-fits-all guideline-based approach to asthma management, which involves inhaled corticosteroids and  $\beta_2$ -agonist therapy, is the inability to prescribe precision treatment according to specific pathways or phenotypic groups. Treatments differ in their effects on symptoms, airway inflammation, and the risk of attacks<sup>80,89</sup> (table 4), and so a precision approach would seem more logical. This approach might avoid both inappropriate overdosing of inhaled corticosteroids in

symptomatic patients with non-eosinophilic asthma, including the obesity-associated phenotype,<sup>25,126</sup> inappropriate undertreatment with inhaled corticosteroids in patients with severe eosinophilic asthma, and inappropriate overdosing with maintenance longacting  $\beta_2$ -agonist therapy in asymptomatic patients with relatively fixed airflow obstruction.

The precision approach we advocate addresses the problems associated with the treatment of patients with the poorly defined asthma COPD overlap syndrome, whereby undue emphasis on the COPD component could lead to risks from sole bronchodilator long-acting  $\beta_2$  agonists or long-acting antimuscarinic therapy, whereas undue emphasis on the asthma component could lead to unnecessary side-effects from inhaled corticosteroid therapy and inadequate bronchodilator therapy. This difficulty could be avoided if the airway disease in the individual patient is deconstructed, and treatable traits are treated, without considering diagnostic silos.

Furthermore, alternative treatments to inhaled corticosteroids and  $\beta_2$  agonists might be preferable in selected patients. Specific responder groups have not been identified for established treatments such as theophylline, leukotriene receptor antagonists, and long-acting antimuscarinic drugs, or potential treatments directed against latent infection or antioxidant stress. Further investigation of pathways, and consequently biomarkers, to identify responder groups to therapeutic drugs similar to the approach used with inhaled corticosteroids and monoclonal antibody therapies represents a priority. Another research priority is to investigate the effects of novel pharmacological and vaccine treatment approaches to modify the natural history of the different phenotypes included in the spectrum of asthma.

*Improved monitoring and new treatment frameworks*

Unfortunately, recommendations for monitoring patients with asthma often also conform to the one-size-fits-all approach. Should the monitoring approach be tailored to the specific phenotype of the patient? Monitoring should be considered as an adaptive process, whereby changes in the phenotype, drug response, adherence, developmental aspects in children, and disease stability are constantly re-assessed (figure 7). The medical history of patients should be considered by the physician for treatment decision making.

Once established on treatment, monitoring is an iterative process whereby symptoms and risk of adverse outcomes (ie, attacks) are assessed and management is fine-tuned. As symptoms due to airflow limitation and risk as a result of active eosinophilic airway inflammation are the most important and recognisable treatable traits in patients with airway disease, the schema shown in figure 7 would be sufficient in most circumstances and should be applicable in primary care and other

non-specialist settings.<sup>183</sup> Failure to achieve an acceptable level of control in one or more domains should prompt a more specialist review, with attention focused on other pulmonary and non-pulmonary components as shown in tables 4–6. Two immediately obvious scenarios in which failure to achieve control is likely are those of patients with symptoms not due to airflow limitation and patients with recurrent exacerbations with low concentrations of biomarkers of eosinophilic airway inflammation. Cough reflex hypersensitivity is an important cause of symptoms in the absence of airflow limitation and infection-associated neutrophilic airway inflammation in individuals with low biomarkers of eosinophilic inflammation is an important cause of recurrent attacks. One advantage of the approach outlined in figure 7 is that the different underlying reasons for symptoms and attacks become apparent early in the diagnostic process rather than after many months of futile and escalating inhaled treatment.

Several randomised controlled trials<sup>10,11,26,27</sup> have shown that the precision medicine approach to treatment and monitoring in adult asthma is superior to conventional stepped-up therapy in well resourced countries. In low-income and middle-income countries, the priority is to ensure that basic therapy is available in every community (figure 6). Once this goal has been achieved, we suggest that the approach shown in figure 7 is also likely to be useful although it would require adaption for use in low-income and middle-income countries. The approach we propose does not make the assumption that asthma in Africa is the same as in London; indeed, in view of the much greater and more disparate burden of childhood infections in low-income and middle-income countries, the diseases might be very different.<sup>184,185</sup> This disparity represents another example of why the use of umbrella terms for asthma across the globe is problematic.

However, several important unresolved issues remain. The first key question is how stable are the eosinophilic and non-eosinophilic asthma phenotypes and whether simple biomarker assessments (eg, blood eosinophil and FeNO, which are predictive of a response to inhaled corticosteroids) will consistently identify these groups.<sup>186</sup> The associated clinical question is whether inhaled corticosteroids can be safely withheld in patients with a specific biomarker profile. This highlights a key feature of the proposed framework—the need for stratification in planning treatment. Some patients with objectively documented episodic asthma might be eosinophilic at one point in their life but not at another,<sup>187</sup> but it might be difficult to distinguish episodic asthma and airway eosinophilic inflammation without repeated objective evaluation. Overestimation of control and difficulty understanding symptom patterns over time might present additional difficulties, particularly in paediatric care, whereby the history is primarily obtained from a third-party (ie, parents) or from children. The pragmatic solution might be to use intermittent or regular

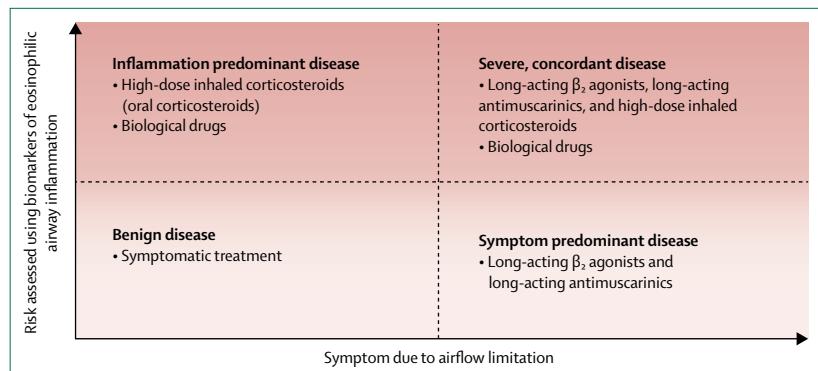


Figure 7: Ongoing monitoring of the two dominant treatable traits of airways diseases and precision management

Combination corticosteroid and rapid-onset  $\beta_2$  agonist inhaler is the default rescue medication.

low-dose inhaled corticosteroids in a combination inhaler with short-acting  $\beta_2$  agonists or rapid-onset long-acting  $\beta_2$  agonists in such patients.

The second key question is what treatment to use instead of escalating doses of inhaled corticosteroids in patients with non-eosinophilic obstructive airway disease. Monotherapy with long-acting  $\beta_2$  agonists has been shown to increase the risk of mortality in patients with asthma.<sup>188</sup> Although this risk might be exclusive to patients with an eosinophilic pattern of disease, definitively obtaining evidence of this might be difficult. We therefore suggest that as-required inhaled corticosteroids and short-acting  $\beta_2$  agonists or rapid-onset long-acting  $\beta_2$  agonists as combination inhaler therapy is the default treatment in patients with variable symptoms or airflow limitation, but the inhaled corticosteroids dose should not be escalated unless biomarkers of eosinophilic airway inflammation are raised (figure 7). Long-term treatment with low-dose macrolide antibiotics has been shown to be effective in small studies of non-eosinophilic asthma,<sup>152,153</sup> but patient side-effects and concerns about global antibiotic resistance restrict their widespread use. The use of alternative treatments, such as theophylline, leukotriene receptor antagonists, and long-acting antimuscarinic drugs, has not been examined in detail in this patient group, thus making specific recommendations is difficult.

The validity of the cutoff points at which prescribers and patients move up or down to the next step in treatment is a crucial aspect of the current approach to asthma treatment. Arguably, the stage at which low-dose inhaled corticosteroids are prescribed is the most important, and this therapeutic approach has been recommended by previous guidelines for patients who use their short-acting  $\beta_2$  agonists on more than two occasions per week,<sup>36</sup> and (on the basis of increasing evidence), on two or more occasions per month.<sup>37,189</sup> However, international surveys<sup>190</sup> have shown that doctors do not recognise the need for inhaled corticosteroids therapy at such stages, and patients and

clinicians usually overestimate control. Furthermore, if prescribed, adherence to inhaled corticosteroids might be as low as 20%, which is not surprising because patients are required to take treatment twice a day, regardless of whether they have symptoms.<sup>191</sup> The fact that patients with intermittent or mild asthma are unlikely to be adherent with regular inhaled corticosteroids treatment might make prescribers reluctant to issue a prescription. However, poor adherence is associated with considerable asthma-related morbidity: the risk of an asthma exacerbation is more than three times higher in patients after stopping low-dose inhaled corticosteroids.<sup>192</sup>

Recognition of this problem has led to the consideration of methods that are applicable in primary care that might improve inhaled corticosteroid adherence, and alternative regimens to that of short-acting  $\beta_2$  agonists monotherapy for symptomatic relief in intermittent asthma. The biomarker directed approach shown in figure 7 might help clinicians to make a definitive treatment decision and encourage patients to commit to that treatment. At present, the first step is the use of short-acting  $\beta_2$  agonists as required, which is only logical if symptoms are exclusively due to intermittent constriction of airway smooth muscle. Patients with concomitant, albeit low-grade eosinophilic inflammation, also require treatment, perhaps using a combination corticosteroid and a fast-onset  $\beta_2$ -agonist inhaler solely as reliever therapy. The use of these two treatment options as the first step for intermittent asthma have been debated,<sup>9,193</sup> but what is needed is not a sterile debate about possibilities, but measurements of the problem and precise treatment, even for apparently mild disease. Substantial rationale exists for a regimen that uses symptom-driven  $\beta_2$  agonist use as the vehicle for inhaled corticosteroids delivery and allows self-titration of inhaled corticosteroids dose according to changes in asthma control.<sup>9</sup> However, this approach (as do many current management frameworks) depends on symptom perception, which is notoriously poor in patients with asthma, and which is also poorly diagnosed by their clinicians. A proof of concept study<sup>194</sup> in adults with intermittent and mild asthma has shown that the symptom-driven use of combination inhaled corticosteroids and short-acting  $\beta_2$  agonist medication achieves similar efficacy to regular inhaled corticosteroids therapy, and leads to fewer severe exacerbations compared with short-acting  $\beta_2$  agonist reliever therapy alone. In children, the TREXA study<sup>195</sup> showed that during the process of stepping down treatment, intermittent combined inhaled corticosteroids and short-acting  $\beta_2$  agonists were more effective than short-acting  $\beta_2$  agonists alone, with fewer side-effects than continuous low-dose inhaled corticosteroids, albeit at the expense of slightly lower lung function. Because treatment with long-acting  $\beta_2$  agonist monotherapy

(particularly in those with eosinophilic airway inflammation) should not be used for asthma, the use of short-acting  $\beta_2$  agonist monotherapy in mild asthma of this phenotype should be questioned. Further investigation of combination inhaled corticosteroid and short-acting  $\beta_2$  agonist and combination inhaled corticosteroid and fast-onset long-acting  $\beta_2$  agonist reliever therapy for intermittent and mild asthma represents a priority and will determine whether single inhaler therapy might be possible across the spectrum of asthma severity, initially with a single combination corticosteroid and fast-acting  $\beta_2$ -agonist inhaler used as reliever therapy only, progressing to both maintenance and reliever therapy.

From a therapeutic perspective, combination inhaled corticosteroid and fast-onset long-acting  $\beta_2$ -agonist therapy prescribed according to the maintenance and reliever regimen reduces the risk of severe attacks by about 40–50% compared with prescribed combination inhaled corticosteroid and long-acting  $\beta_2$ -agonist maintenance and short-acting  $\beta_2$ -agonist reliever therapy, despite similar efficacy for other outcome measures such as lung function and asthma control.<sup>196,197</sup> The efficacy of this approach, and of a biomarker directed approach, is particularly obvious in patients in whom the risk of asthma attacks is increased<sup>198</sup> and perhaps in poorly adherent patients.<sup>199</sup> This evidence underlies the preferred use of combination corticosteroid and fast-onset  $\beta_2$ -agonist inhaler therapy (prescribed as required or according to the maintenance and reliever therapy regimen) in patients requiring therapy for documented episodic disease. Since the maintenance and reliever therapy approach is based on the hypothesis that an increase in asthma symptoms is due to increased eosinophilic airway inflammation, which responds well to additional doses of inhaled corticosteroids within the combination inhaled corticosteroid and fast-onset long-acting  $\beta_2$ -agonist reliever regimen, this approach might be most applicable in patients with eosinophilic asthma. However, a population of patients in whom inhaled corticosteroids can be safely withheld would be difficult to identify, and thus the adoption of this approach generally might be reasonable.

#### *Better understanding of the dose-response relationship with inhaled corticosteroids*

The classification of low, moderate, and high daily doses of inhaled corticosteroids in existing guidelines needs revision. In adults, the current classification states that 100–250 µg fluticasone propionate per day represents a low dose, which disregards evidence that 90% of the maximum obtainable therapeutic benefit is achieved with a fluticasone propionate dose of 250 µg per day,<sup>200</sup> or the fact that initiation of inhaled corticosteroids therapy at daily doses above 400 µg budesonide or equivalent has shown no improvement in efficacy compared with lower doses.<sup>201</sup> In children, the BADGER study<sup>202</sup> showed that

few patients improved when the dose of fluticasone propionate was increased above 100 µg twice daily. Further investigation of the inhaled corticosteroids dose-response relationship for both efficacy and systemic adverse effects is required, particularly in children. However, this plateau might be dynamic. For example, in patients in whom considerable pro-inflammatory drive exists—eg, from exposure to aeroallergens to which the patient is sensitised and cannot avoid—relative steroid resistance might occur leading to the requirement for larger and more frequent doses of inhaled corticosteroids.<sup>203</sup> This underscores the value of the approach described previously, to not consider airway disease in isolation, but also in the context of the environment. Systemic absorption of high-dose inhaled corticosteroids is lower in patients with inflamed airways than those without inflammation,<sup>204</sup> which might be relevant as it is possible that systemic corticosteroid therapy is necessary in some circumstances. For example, the systemic contribution to eosinophilic airway inflammation, as reflected by the blood eosinophil count, might be so high that small changes in recruitment signals in the airway, or the involvement of recruitment pathways not inhibited by inhaled corticosteroids, lead to considerable worsening of airway inflammation. This possibility is supported by the beneficial effects of depleting circulating eosinophils with anti-interleukin 5, and the very close association between clinical benefit of treatment and pre-treatment blood, but not sputum, eosinophil count.<sup>12</sup> If this model is correct, any benefit of high-dose inhaled corticosteroids might be a direct result of systemic activity and thus could be achieved more cheaply and just as safely with a small dose of oral corticosteroids.

#### Better technology

An important aspect of asthma management is the proper use of medication delivery devices and adherence. In this context, the continued, widespread use of metered dose inhalers without spacers represents complacency, in view of how easy it is to use them wrongly, and how inefficient they are even when used correctly. We propose that beyond the use of metered dose inhalers with spacers in the very young (aged <3 years), elderly patients with coordination problems, individuals who need high doses of inhaled corticosteroids (likely far fewer individuals than those prescribed them), and possibly in low-income and middle-income settings for financial reasons, a case should be made to ensure universal use of modified inhalers that can only be activated when attached to a spacer. To tackle adherence, devices need to detect not merely activation but also inhalation and its adequacy, with daily feedback to the patient and the physician, with alerts when medication is not taken. Research is needed to better understand patients' responses to these devices and this type of monitoring. The clinical community appear content to use outdated technology to deliver medications.

Consequently, metered dose inhaler technology has not progressed in 25 years. Thus, the fact that we do not effectively use the medications available is not surprising.

Although individual therapeutic trials are not recommended as a basis for long-term treatment decisions, such trials are inevitable in at least some contexts (eg, wheeze in children aged younger than 5 years). However, progress can be made beyond prescribing an inhaler and assessing whether it worked after a 6 week trial. These n-of-1 trials should be placebo controlled and double-blind and should incorporate electronic monitoring of adherence, including technical adequacy of the inhalation technique.

#### *21st century asthma clinics*

Considering asthma management in a broader context, methods to enhance the patient and health-care provider partnership are often neglected. Basic principles, such as regular checking of inhaler technique and the implementation of a guided asthma self-management system of care, remain a core component of asthma management.<sup>37</sup> One of the important concepts of asthma management plans is the requirement to look at overall, day-to-day management of the condition in a unified manner, and not to focus only on the management of asthma attacks, or to assume that asthma attacks are inevitable. In practice, outpatient consultations have not changed in over a century; a brief face-to face-consultation with an individual with a medical degree and variable knowledge of the patient and the disease, who might or might not have access to the previous notes. The challenge now is to use advances in information technology and communication, which have been underused in the past, to improve such partnerships in an evidence-based and cost-effective manner. Young individuals use social media to communicate many times a day; why do we not use this platform in health care? A smartphone app can be used to monitor how many steps someone has walked in a day, thus apps could be used to monitor airway disease continuously and in real time, obviating the need for patients to perceive symptoms. Evidence<sup>205</sup> indicates that this sort of approach works and even in low-income and middle-income countries many individuals have smartphones, which could be used to improve access to health care.

#### **Wheezing illnesses across the ages**

##### **Where are we now?**

The evolution of airway function in patients between the first and tenth decade has been illustrated by curves produced from almost 100 000 cross-sectional observations (panel 6). These curves and other data highlight three key stages of life in which abnormal lung development can affect long-term risk of airways disease: birth, childhood, and after age 25 years. First, normal lung function should be confirmed at birth because abnormal lung function at birth or in patients younger

**Panel 6: Important findings of birth cohort studies**

- Transgenerational factors (eg, grandparents smoking) increase the risk of airway disease.<sup>138</sup>
- Antenatal factors such as exposure to tobacco smoke<sup>146</sup> and pollution<sup>144</sup> affect airway disease in the fetus by affecting gestational age and birthweight, through direct effects on lung structure, and through effects on the fetal immune system, which lead to abnormal responses to allergens and viruses.<sup>145</sup>
- Location of birth (home vs hospital<sup>106</sup>) and mode (vaginal vs caesarean section<sup>64</sup>) of delivery might affect the risk of future airway disease.
- In the immediate postnatal period, further decline in lung function occurs in individuals who develop persistent wheezing illnesses, particularly in neonates with airway hyper-responsiveness.<sup>67</sup>
- Antenatal and postnatal environmental microbial exposures (farm animals, dogs, siblings, day care) modulate the risk of childhood asthma by affecting atopy, responses to viral infections, and skewing immune responses.<sup>71,207,208</sup>
- Postnatally, passive smoking,<sup>63</sup> pollution,<sup>144</sup> moisture damage,<sup>209</sup> obesity,<sup>210</sup> pesticide exposure,<sup>211</sup> and multiple early atopic sensitisation<sup>72,74</sup> increase asthma risk.
- Five childhood risk factors (maternal or paternal asthma, maternal smoking, childhood asthma and respiratory infections) account for at least half the risk of developing chronic obstructive pulmonary disease (COPD) in later life.<sup>137</sup>
- Lung function tracks over many decades: in most circumstances no catch-up lung growth is observed.<sup>140</sup>
- Airway disease in children aged younger than 5 years might recur after quiescence in adulthood or manifest for the first time in adulthood.<sup>58</sup>
- Adolescent girls with premature menarche might have an increased risk of developing asthma.<sup>212</sup>
- Multiple trajectories to COPD have been identified. A longitudinal analysis<sup>140</sup> showed that of the individuals with a forced expiratory volume in 1 s of 80% or higher in early adult life, 158 (7%) of 2207 had a rapid decline in lung function and developed COPD. Another group had a forced expiratory volume in 1 s of less than 80% in early adult life, and 174 (26%) of 657 developed COPD with normal rates of decline in lung function on spirometry. Both trajectories contributed equally to the burden of COPD, although the trajectories differed in the rate of decline in lung function in later life.<sup>140</sup> Subsequently, follow-up of the CAMP study bridged the gap between adult and childhood studies.<sup>213</sup> Four asthma spirometry trajectories were identified, comprising combinations of normal or reduced plateaux of lung growth, and normal or early decline in spirometry, independent of treatment prescribed (nedocromil, budesonide, or placebo).
- In the many large studies<sup>214–217</sup> of spirometry in adult life, no single environmental factor, including smoking, consistently predicted an accelerated decline.

than 5 years tracks into the third decade of life at least. Second, normal growth in lung function should be confirmed during childhood until a plateau is reached between the age of 20 and 25 years. Third, in individuals older than 25 years, normal lung function should be confirmed because accelerated decline in lung function after this age leads to poor lung function in later life.

Many overlapping birth and other cohorts have been studied, in some cases with follow-up over several decades (panel 6).

In early life, as a clinical community we need to move on from irrelevant questions regarding the age at which asthma can be diagnosed (which is neither a single diagnosis nor an intelligent question) and instead,

consider the treatable traits of airway disease.<sup>61,129</sup> Doctors still argue about what is bronchiolitis, what is viral wheeze, and what is asthma in early life without defining terms clearly, and no biomarkers are available to differentiate them. Viruses are known to be an important trigger of attacks of wheeze,<sup>163,164</sup> but all viruses are assumed equal, and equally treatment resistant, on the basis of a small amount of data.<sup>218</sup> Evidence<sup>67</sup> has shown that children with eosinophilic airway inflammation and variable airflow obstruction between the age of 5 and 16 years have airflow obstruction at birth or during early life, but with the exception of targeting tobacco smoke and pollution (in a half-hearted manner), how to prevent these abnormalities remains unclear. Aeroallergen sensitisation (in particular, multiple early sensitisation) in the same time period is associated with ongoing symptoms and loss of lung function and persistent airway hyper-responsiveness,<sup>72</sup> but no prevention methods are available, despite the fact that airway function tracks from a young age (<5 years) to late middle age, which indicates that the first 5 years of life are crucial. Early viral infections, such as rhinovirus or respiratory syncytial virus infections, cannot be prevented in most children, and anti-respiratory syncytial virus approaches have produced mixed results.<sup>219,220</sup> Furthermore, the clinical field is inundated with irrelevant questions, such as: do children with sickle cell disease, bronchopulmonary dysplasia, and other causes of wheeze have asthma? Instead, we should try to establish the specific nature of airway disease in terms of the traits shown in table 4.

Knowledge of the developmental trajectories of asthma is poor. Multiple prospective cohorts have established patterns of wheezing going forward from infancy, and from a series of overlapping cohorts, the clinical significance of early wheeze has been established in adult life (panel 6). However, these studies were in large populations, and by definition were non-invasive, and thus provide little information about the developmental changes in mechanisms. For example, atopy-associated asthma in children aged between 5 and 16 years is assumed to be driven by the same pathways as that in adults, however, some evidence indicates that in severe asthma, the innate epithelial cytokines and lineage negative innate lymphoid cells might be more important in children than in adults (figure 5).<sup>149,221</sup> Furthermore, classical adult asthma phenotypes and complications (eg, aspirin-sensitive asthma, allergic bronchopulmonary aspergillosis, occupational asthma, late-onset asthma) remain in adult silos, with few attempts to understand whether these conditions have their origins early on; despite evidence<sup>222</sup> that women with so-called late-onset asthma actually had important symptoms and physiological abnormalities in early life. Indeed, the term late-onset prejudices the issue, and discourages any consideration of probable early origins.

Recall of major childhood respiratory illnesses (eg, pneumonia, pertussis, recurrent wheezing, or so-called

recurrent bronchitis) is poor, with these illnesses being forgotten or conversely, wrongly recalled as having been present in interviewed adults.<sup>222,223</sup> In the context of interstitial lung disease, data has shown the same gene mutation (surfactant protein C) in the same family can cause different diseases—neonatal pulmonary alveolar proteinosis<sup>224</sup> and adult-onset pulmonary fibrosis<sup>225</sup>—presumably associated with modifier genes and environmental exposures. Animal data<sup>226</sup> indicate that transient exposures during key phases of development (eg, neonatal hyperoxia) might affect responses to allergens and viruses in adult life. Thus, some of the adult phenotypes that are not observed in childhood might in fact be manifestations of a condition that causes a completely different early airway disease. These age windows might represent a key opportunity for disease-modifying treatment or primary prevention strategies. A prospective study with a birth cohort large enough to investigate these relatively uncommon adult phenotypes is unlikely, and even if such a study began, the results will only be of interest to future generations, therefore, a different approach is needed.

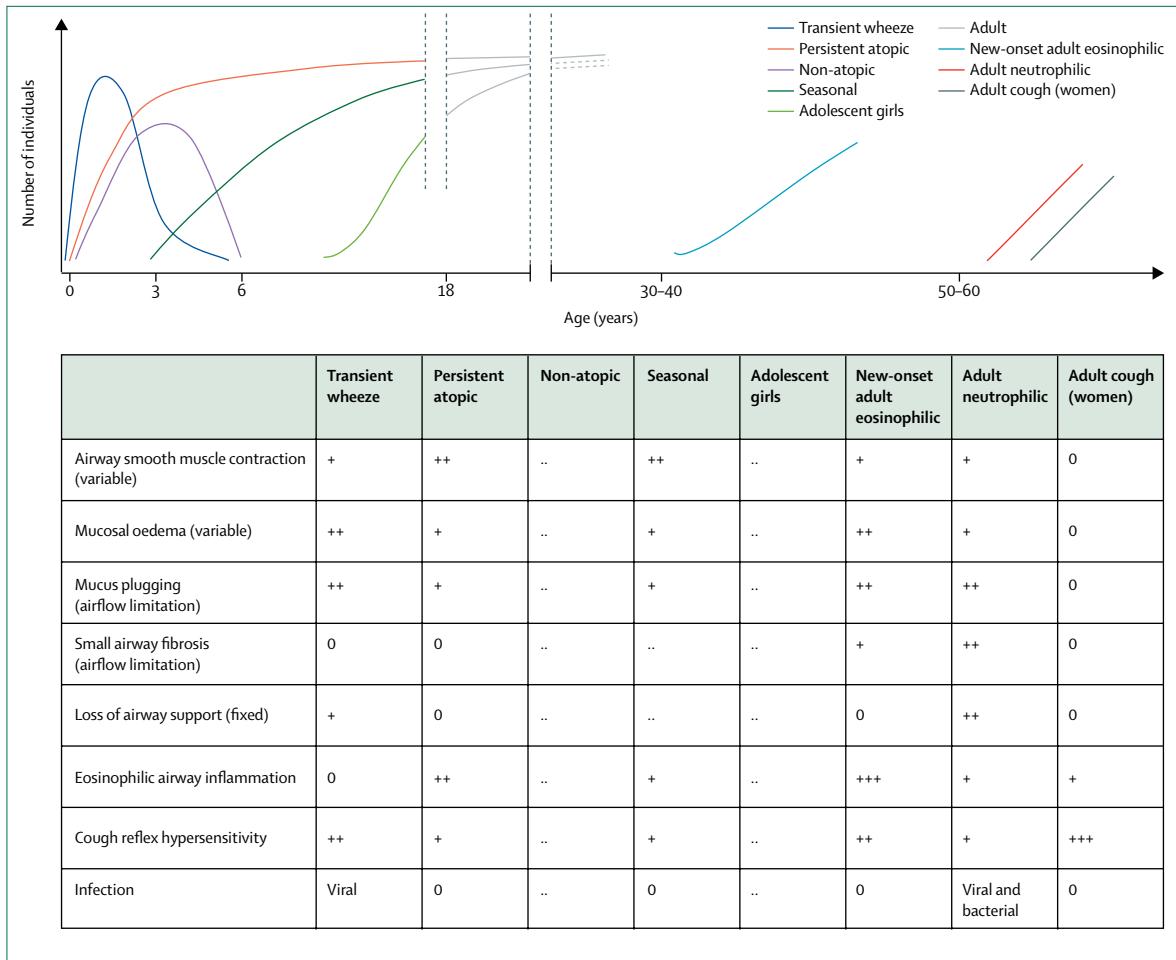
The evolving clinical picture of airway disease is characterised by a multitude of genetic and environmental risk factors with small effects and a large phenotypic variability, particularly in early childhood. Causal relationships between the multitude of small effects and phenotypic variability are unclear. Li and colleagues<sup>227</sup> postulated that small risks might be compounded in adult life, with the number of risk alleles being associated with the probability for the occurrence and extent of asthma severity. Furthermore, the effects of a specific risk allele might be magnified by an adult life exposure (eg, occupational exposure) or become relevant during lung ageing (eg, impaired airway development between birth and age 5 years).

However, the development of the respiratory system in early childhood is complicated by growth processes and adaptation to changing environments, including the transition from an intrauterine to extrauterine environment. Complexities also occur in the ageing adult because of age-associated senescence. Although some outcomes might be the result of a cumulative effect, complexity theory suggests that these mechanisms and interactions are likely to be far more complex, non-linear, and remain not merely unknown, but not even considered. Interactions can only be hypothesised on the basis of general principles inherent in complex systems biology, such as degeneracy.<sup>228</sup> Degeneracy in systems biology refers to the ability of alternate structural pathways to exhibit similar or dissimilar functional outcomes depending on context. Frequently mislabelled as redundancy, degeneracy refers to structural variation, whereas redundancy refers to structural duplication. Degeneracy has been described in the immune system,<sup>229</sup> the control of breathing,<sup>230</sup> and human movement analysis.<sup>231</sup> For adaptive, complex systems, degeneracy

has several benefits—eg, structural variation improves robustness to perturbation by an environmental stimulus and allows for adaptability.<sup>232</sup> In the developing respiratory system, complex behavioural adaptations might be necessary to adapt to changing environmental conditions from fetus to adulthood. In view of such an effect, the overall risk of asthma might not always simply be the result of cumulative, individual asthma risk factors, and a much more sophisticated mathematical and modelling approach will be needed. This putative multitude of non-lethal small effects might have contributed to the evolution of a greater heterogeneity of phenotypes than has previously been considered, in view of the need of humans to adapt to a diverse environment.

Despite the complexity of numerous small effects and large variability in asthma occurrence, some common themes have emerged. Highly descriptive patterns of wheezing during early childhood have been strikingly consistent across birth cohorts. Figure 8 shows recognised wheezing syndromes by age, with suggested major treatable traits. Machine learning approaches have been successfully applied to the study of atopy,<sup>75,233</sup> once considered an all-or-nothing occurrence. Only the latent class of early multiple atopic sensitisation (but not any other sensitisation classes) in the Manchester and Isle of Wight studies<sup>75,233</sup> was associated with a worse trajectory of lung function, particularly if associated with acute attacks of wheezing.<sup>39</sup> Clearly, the complexities of asthma trajectories cannot be described in simple terms, or by single cross-sectional measurements, and conclusions drawn from cross-sectional analyses of longitudinal data might not accurately reflect longitudinal trajectories within individuals.<sup>234</sup> Moreover, although instrumental in understanding predictors of disease trajectory, wheezing trajectories are difficult to apply prospectively and have not been used to explore treatment response, let alone genetic and environmental determinants or biological markers of these trajectories. What remains unclear is why asthma develops in some contexts (and might or might not apparently resolve), and in other individuals health is maintained. Several subsystems are likely to be involved in this complex disease, interacting in a network-type manner. These subsystems or compartments include, lung growth and structure, innate immunity (viral infections, mucociliary clearance, surfactant, toll-like receptors) and adaptive immunity (IgE and IgG4, response to infections), allergic sensitisation, epithelial function (barrier and secretory), oxidative stress response, remodelling and repair mechanism, smooth muscle function, metabolic rate and nutrition, interaction with the microbiome, and many others.

Notably, all of these subsystems are influenced by specific genomic and epigenomic regulators, and are similarly altered by environmental factors that might be specific to that compartment.<sup>235</sup> Genomic and epigenomic

**Figure 8: Patterns of airway disease by age and main traits**

+ = weak evidence of involvement. ++ = moderate evidence of involvement. +++ = strong evidence of involvement. 0 = no involvement. .. = no data.

changes have not only been associated with atopy and asthma, but also with factors associated with airway smooth muscle function, lung function, glucocorticosteroid response, effects of prenatal tobacco exposure, air pollution, prenatal sensitisation, stress,<sup>236</sup> and viral infections.<sup>237</sup> On the basis of these considerations, future asthma models need to consider not only developmental gene–environment interactions of the organism, but also those of each compartment, and the network-type interactions between compartments.

**Development of the respiratory system in health and disease**  
In the paediatric context, disease should always be viewed in the context of development and maturation. The relative importance of a specific polymorphism might be age-dependent and might vary with different environmental exposures.<sup>73</sup> Gene expression and epigenetic regulation change with age, and can even be induced during pregnancy.<sup>238</sup> The relative importance of innate and adaptive immune responses changes substantially in the first year of life in response to

environmental antigens and also in the context of asthma.<sup>71,239,240</sup>

The dominant maturational changes in each compartment or subsystem of the body occur at different times. For example, airway size and lung volumes increase until adolescence, whereas the development of the immune system, or the stabilisation of the gut microbiome,<sup>241</sup> is complete by the age of 5 years (hypothesis 1; figure 9). Consequently, if asthma is considered a network response to many weak effects in these subsystems, their relative contribution, or their susceptibility to environmental stimuli, is also likely to change with age (hypothesis 2; figure 10). Age-dependent effects of risk factors on respiratory symptoms have been shown in the context of tobacco smoke exposure,<sup>242</sup> immigration studies,<sup>243</sup> and farming exposure.<sup>244</sup> Maturational programming is likely to be determined by the interactions between intrinsic (eg, growth processes) and extrinsic factors. The system adapts, via a dynamic process involving an exposure, the host's response to the exposure, and the subsequent adaptation of the host's

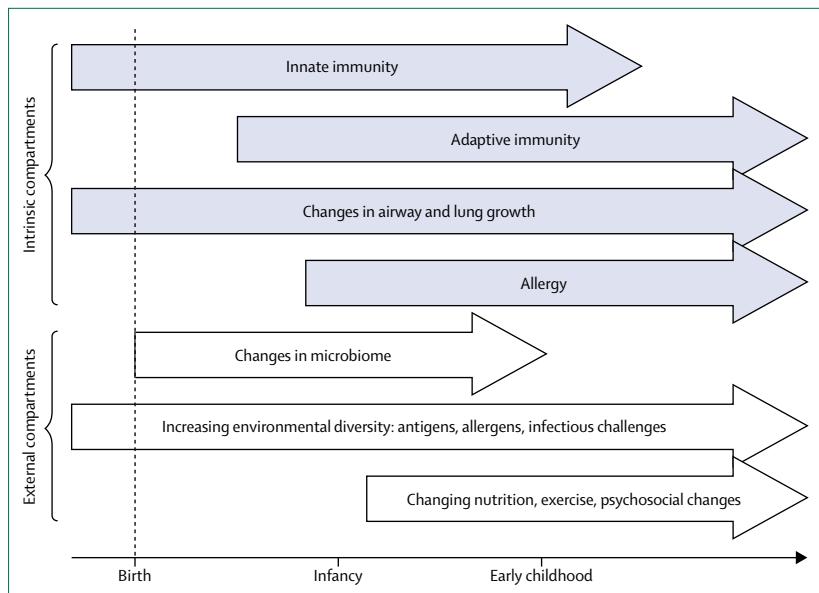
system to the exposure (plasticity). Adaptation works well if the subsystem functions optimally in the new context. In most individuals, these maturational processes will result in an adapted, healthy condition.

The biological consequences of adaptive processes in asthma-related diseases are still poorly understood. A 2014 model<sup>245</sup> suggested that the gene–environment interaction establishes the asthma phenotype in early childhood. Thus, the relative contribution of a specific compartment could become dominant at a specific age, and could determine the phenotype. We hypothesise that the evolution of asthma might be an aberration of one or many different interacting compartments (hypothesis 3; figure 11). The compartments involved in the transient wheezing phenotype might include, among others, airway size and innate response to viral infections. By contrast, persistent wheeze could be an early aberrant stabilisation in response to disease, which might impede subsequent healthy maturation. Intermittent phenotypes might manifest as altered states of stability in response to environmental exposures or unrecognised persistent disease between attacks.

### Where do we want to go?

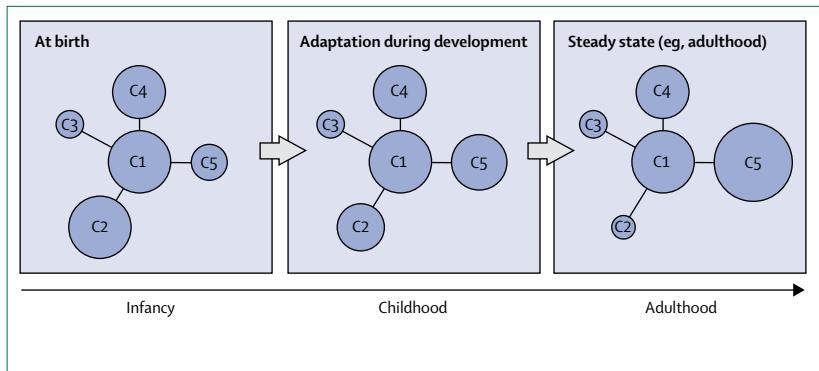
Cross-sectional studies cannot investigate asthma disease trajectories. Future studies would thus need to assess key components of the disease process with a multidimensional or even multilevel (gene–molecule–cell–organ) approach, and the interaction between them to quantify their relative contributions. How genes and environmental factors affect the key compartments that lead to cumulative or even crucial effects in the context of development needs to be understood. Such network-type analyses are well known in systems biology. Thus, a step change is needed in longitudinal studies, using well-defined outcomes that reflect the various compartments (lung function, immunological, inflammatory, metabolic, genetic, epigenetic). Furthermore, systems medicine often neglects the idea that the clinical phenotype, and thus the related endotype, can be changed by the environment. In a syndrome such as asthma, in which symptoms are strongly determined by interaction with the environment, quantification and characterisation of an individual's response to the exposome (ie, every exposure to which an individual is subjected from conception to death) is crucial.<sup>246</sup> Paediatricians could learn a great deal from adult occupational health physicians in this setting with regard to asthma.

Clearly, even if a new birth cohort study that addressed these complexities were to commence today, it would be many years before new information was in the public domain, by which time interest would likely have shifted to a new area of research. Therefore, existing longitudinal and cross-sectional studies should be used innovatively. For example, a detailed biological signature of individuals with rapid decline in lung function in adult life<sup>140</sup> should



**Figure 9: Asthma development (hypothesis 1)**

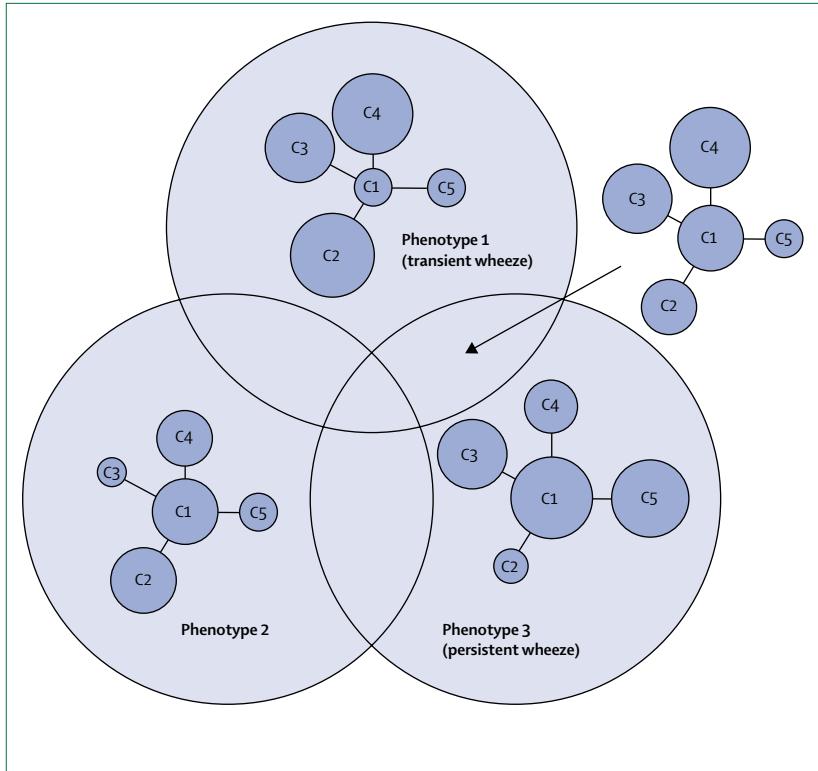
The relative contribution of risk factors to the risk of asthma in later life is composed of a multitude of small effects. The small effects originate from various subsystems or compartments (eg, immune system, airway growth, epithelial function). Each subsystem has unique timeframes and phases of development. The relative importance of these subsystems for asthma (arrows) might be age-dependent. Susceptibility (window of opportunity) to environmental stimuli is likely to vary at different ages for each compartment. The overall temporal evolution of health and disease will be affected by the complex temporal interplay of these compartmental subsystems.



**Figure 10: Asthma development (hypothesis 2)**

Because not all compartments of the respiratory system reach maturity at the same age, the relative contribution (indicated by circle diameter) of each compartment (C1–C5) to the function of the respiratory system might change during development. For example, the importance of small airway size (compartment C2) will decrease with age for wheezing disorders, whereas other key compartments, such as the immune system (compartment C5) in the sensitised child, will become dominant with increasing age.

be compared with the same parameters earlier in life, to determine whether this group can be detected early, at a time when an intervention might prevent later deterioration. One example is serum CC16, which is associated with reduced lung function in childhood, and accelerated decline in lung function during adulthood.<sup>247</sup> These different associations could represent a two way process—are early biological phenotypes and signatures associated with later phenotypes? Some cohorts had no early microbiome studies, but late middle age samples



**Figure 11: Asthma development (hypothesis 3)**

Depending on how environmental stimuli affect or even alter the development of the various compartments, the phenotypical expression of the disease might be different as well as age-dependent. As shown in this model, the contribution to the overall disease risk of small airway size (C2) and sensitisation to any allergen (C5) is quantitatively different in transient wheeze (phenotype 1) compared with persistent wheeze (phenotype 3). Thus, in a large population of patients with asthma, overlaps between distinct asthma phenotypes are likely.

could be obtained, which could be compared with samples from cohorts in childhood and early adult life, as well as being explored in animal models. This approach is not the scientific ideal, but it represents a pragmatic approach to understanding longitudinal biological complexity.

To develop preventive strategies the pathways in which early life events affect lung function in the long term need to be understood. Factors that prevent or reverse adverse changes need to be identified, and understanding normal lung development might be a prerequisite. Basic science could help with the development of better animal models with long-term observations in the growing animal, and studies that investigate the interactions between a multitude of small triggers, rather than single triggers (eg, house dust mite exposures). Epidemiologists and basic scientists need to emerge from their silos to codesign these models. These models need to use network-type analyses to assess the key compartments and pathways, their interactions, and their relative contributions to asthma, to establish how these interactions result in cumulative or even crucial effects during various phases of development.

If these ideas are correct, more complex epidemiological studies need to be developed. However, better scientific understanding is needed before a new birth cohort study can address the complexity of these questions. The challenge is to find ways of monitoring compartmental function, and gene–environment interactions that are acceptable in large, longitudinal, population-based studies. The challenge is also to search existing cohorts for data that could be used to provide insights into these complexities; in this context, the harmonisation of cohorts into large datasets, such as the Study Team for Early Life Asthma Research e-lab,<sup>248</sup> are particularly welcome. Research should shift from a pulmonary focus, and consider whether other organs (eg, the cardiovascular, endocrine, metabolic, or neurological systems) might have also had similar developmental abnormalities.<sup>249</sup> Small reductions in lung function and birthweight are associated with disproportionately increased mortality rates: are these warning signs for the whole body?

From a clinical perspective, the focus is on targeting the immediate disease manifestation, which fails to address three basic questions:

- What was the developmental trajectory to the current status?
- What are the current components of the airway disease?
- What will be the onward developmental trajectory from here?

Only this sort of approach offers the opportunity to move asthma treatment beyond palliative care.

## Beyond palliative care: towards prevention and cure

### Where are we now?

The greatest unmet need in asthma is generally considered to be the requirement for more effective therapeutics for patients with chronic asthma who are refractory to currently available treatments. Although this requirement understandably resonates with treating physicians and their patients, the blanket acceptance of this need as the number one priority across a substantial proportion of the asthma research community, and among drug developers, health-care providers, and regulatory authorities, serves to perpetuate what has become accepted in developed (and increasingly in developing) countries: the inevitable progression from intermittent early childhood wheeze to persistent asthma in adolescence, followed by lifelong therapeutic drug dependence.<sup>250</sup> From a public health perspective, the greatest unmet need in asthma is radically different: the absence of safe and effective treatments for primary or secondary prevention of asthma that can be used as early as possible in the disease process.

Guideline groups are partly responsible for the low priority afforded to primary prevention strategies. Because guidelines focus on established asthma, and not the

fundamental underlying causes, these recommendations have set the agenda for asthma as a disease to be controlled not cured, without attempting to devise early intervention strategies to prevent progression to this state.

Disease control-based care has informed much so-called innovation in asthma. The focus of control-based care has been on newer and more potent inhaled corticosteroids and once daily long-acting  $\beta_2$  agonists, which can be characterised as merely more of the same. Do we really need more inhaled corticosteroids? Should the National Institute for Clinical Excellence and other regulatory authorities put a blanket ban on licensing any new inhaled corticosteroids or long-acting  $\beta_2$  agonists unless they are cheaper than, and at least as effective, as the drugs that are already available? Also, increasingly potent inhaled corticosteroids might be harmful. The airway mucosa has and requires sophisticated immune defence mechanisms against pathogens and other inhaled irritants, and inhaled corticosteroids increase the risk of pneumonia, tuberculosis, and atypical *mycobacterium* infection.<sup>113</sup>

New inhaled corticosteroids have led to spiralling costs of asthma treatment, which seem set to continue rising despite evidence of diminishing returns.<sup>21</sup> Are the newly formulated inhaled corticosteroids really any better than beclometasone? Some individuals have previously argued<sup>250</sup> that the continuation of this trend is inevitable unless a substantial realignment of entrenched drug development policy is implemented in the pharmaceutical industry, and a parallel shift in licensing policy by regulatory authorities is enforced to encourage the development of drugs that can halt the progression from acute to chronic asthma, when the disease first manifests in childhood. A theoretical framework for such an approach, including proof-of-principle data from studies in children with early-stage disease and a range of candidate drugs, already exists.<sup>251</sup> Informed debate on the risks versus potential benefits of this approach is needed.

### Where do we want to go?

Recognition of the differences between the pathways that initiate asthma and those that propagate established disease is key. In early disease, cellular inflammation is absent,<sup>147</sup> and inhaled corticosteroids are ineffective.<sup>76,77</sup> The early pathways of asthma need to be understood in detail, to enable the development of targeted interventions in biomarker detected high-risk groups of babies and infants, with validated biomarkers to assess response.

This issue has not been entirely ignored by the asthma research community: as a result of the efforts of a relatively small number of paediatric-focused groups, in the past two decades progressive data about asthma development from fetal life through to early adulthood has accumulated. Although many questions about the causes of asthma remain contested, these studies<sup>163</sup> are more remarkable for the broad concordance in many of their findings associated with major asthma-promoting

risk factors operative during early life, particularly with regard to the most frequently encountered atopic asthma phenotype. The prominent risk factors were found to be lower respiratory tract infections and particular patterns of sensitisation to aeroallergens, which can act either independently or (more importantly) in concert to trigger episodic cycles of airways inflammation and accompanying wheezing symptoms.<sup>163</sup> The continued recurrence of these inflammatory events, particularly between birth and age 5 years when postnatal lung growth rates are highest, appears to perturb normal maturation of respiratory functions, thus predisposing the development of persistent asthma.<sup>251</sup> Moreover, these same events serve as major triggers for exacerbations once the atopic asthma phenotype becomes established, potentially leading to a vicious cycle of recurrent symptoms with persistently poor airway function. Allergen immunotherapy is the only disease-modifying treatment available; whereas the benefits of inhaled corticosteroids are lost as soon as treatment is stopped, the benefit of three annual cycles of grass pollen immunotherapy for allergic rhinitis has been found to continue for years after cessation.<sup>252</sup>

These findings provide a framework for the systematic testing of a range of therapeutic options associated with primary and secondary prevention, based on the selective targeting of these two interrelated risk factors (lower respiratory tract infections and particular patterns of sensitisation to aeroallergens) that contribute considerably to susceptibility to airway symptoms in early life. In principle, inflammation resulting from the local activation of antimicrobial or atopic pathways arguably constitutes a plausible acute treatment target in infants and young children with recurrent airway symptoms; however, inhaled corticosteroids alone are not going to be the early disease-modifying treatment strategy. Other treatments could be recontextualised for prophylactic purposes in appropriately defined high-risk groups. In this regard, a study of year-long treatment of at-risk children with omalizumab<sup>253</sup> provides proof-of-concept for the role of atopy-associated inflammatory pathways in enhancing the intensity of viral-triggered exacerbations in children with established asthma, and by inference also in comparable infection-related lower respiratory events, which appear to drive early disease pathogenesis in pre-asthmatic infants and children younger than 5 years. Moreover, the successful use of this drug during autumn and winter only to reduce exacerbation frequency in asthmatic children<sup>254</sup> suggests that focusing specifically on known high-risk temporal windows might also be used to further refine prophylactic treatment protocols. An additional example is the bacterial lysate immunostimulant OM-85, which has been previously used for attenuation of infection-associated episodic symptoms in adults with COPD<sup>255</sup> and between birth and age 5 years in individuals with recurrent wheeze;<sup>256</sup> this treatment has recently received

For more on the OM-85  
Australian clinical trials,  
ACTRN12612000518864 and  
ACTRN12614000062628, see  
[www.anzctr.org.au](http://www.anzctr.org.au)

regulatory and national funding agency approval in both the USA (ClinicalTrials.gov NCT02148796) and Australia for use in infants in preventive trials associated with asthma development in later life, and for use on a winter treatment only basis for prevention of exacerbations in children aged between 5 and 16 years.

One difficulty in these and associated trials is determining risk because the positive predictive value of many available indices are poor, although negative prediction is very good.<sup>76,257,258</sup> These predictive indices are based on the crudest markers, which is a recurring theme because the respiratory community has failed to utilise modern omics technology to establish predictive biomarkers, although some progress has been achieved recently.<sup>259</sup> The first major initiative in this regard is targeted prevention of allergic sensitisation in high-risk infants by immune tolerance induction using prophylactic allergen-specific sublingual immunotherapy, with the aim of reducing ensuing asthma development by ages 5–6 years. This trial was downgraded to pilot status after recruitment of only 50 children, enabling subsequent collection of safety data only.<sup>260</sup> However, a conceptually identical trial<sup>261</sup> funded by the National Institute of Allergy and Infectious Diseases, which aimed to prevent allergen-specific sensitisation to food allergen by oral administration of tolerogenic doses of allergen, has successfully achieved its primary endpoints. Additionally, a smaller sublingual tolerance induction trial<sup>262</sup> in the UK funded by the Medical Research Council that targeted prevention of sensitisation to aeroallergens has achieved partial success. This approach clearly shows promise and should be systematically followed up. Encouragingly, several such studies are at the planning stage.

Protecting the growing lung and airways from inflammation triggered by early infections provides even more complex challenges, not least because exposures to certain types of microbial stimuli appear to have beneficial effects.<sup>240</sup> The direct approach of specifically targeting the relevant pathogens is complicated by the following factors: the broad spectrum of viral and bacterial organisms potentially involved, parts of the microbiome are important for early immune development and must be carefully preserved, no relevant vaccines are available, and the potential dangers of bacterial drug resistance associated with overuse of antibiotics. Targeting the problem through enhancement of the overall efficiency of developmentally compromised host defence mechanisms via the use of microbial-derived drugs exemplified by probiotics and prebiotics has been widely discussed, but at this stage the effect size of such treatments seems modest.<sup>263</sup> One issue likely to be associated with this small effect size is the imprecision with which the contents of specific probiotics and prebiotics are known. Emerging data in high-risk infants and children about the use of

orally administered microbial extracts, which function via modulation of the immunoregulatory component of host inflammatory responses, point to alternative possibilities. One recent example is OM-85, discussed previously. Early, but important, data on the effect of fish oil supplementation on the diet has, for the first time, provided compelling evidence of a positive effect on the natural history of childhood wheezing illnesses.<sup>264</sup>

The single factor that hinders progress in this potentially exciting area is the scarcity of relevant paediatric safety data. In this respect, omalizumab is a prime example. This effective biological treatment has been used in adults for 15 years, and yet the necessary safety data in children younger than 16 years, which would open up possibilities for primary prevention trials in high-risk children younger than 5 years, is still not available. The range of potent and increasingly selective type 2 cytokine blockers available for adults with asthma is growing rapidly,<sup>3,29–31</sup> along with other relevant drug classes such as those targeting innate immunity,<sup>265</sup> but drug manufacturers and governmental agencies have expressed little interest in extending this to children, and these groups effectively set the drug development agenda. A fast-track scheme might be useful to move some promising drugs forward in paediatric severe asthma. For this to succeed, paediatric investigators would need to contribute patients, which has been a problem because of increasing bureaucracy within the research environment.<sup>266</sup>

The likelihood of committed researchers leveraging off these emerging advances in therapeutics for prophylactic purposes is depressingly remote. In this regard, federal legislation in the USA dating back to 1998 mandates that the Food and Drug Administration serve to encourage the manufacturers of existing and new drugs for the treatment of established asthma, to test the same drugs in early stage disease in childhood.<sup>267</sup> However, no evidence has suggested that this mandate is effective. Many researchers in this area (on the basis of personal experience from discussions with industry colleagues) can attest that business plans associated with the release of new asthma drugs rarely include a serious paediatric component, and never include prevention. This exclusion will not change unless the clinical, research, and regulatory communities become proactive in arguing this case more forcefully. Remission-inducing and curative strategies might require considerable investment in clinical trials. In the USA, recent curative medicines, such as ivacaftor, have attracted prices in the range of US\$300 000–1 000 000 per patient per year. Will industry be prepared to abandon long-term palliative medications by funding studies that will potentially obviate their need?

In summary, no more me-too medicines should be developed: real effort should focus on shifting from control-based treatment to prevention or cure.

## Attacking asthma attacks

### Where are we now?

Clear terminology is important. Definitions vary and some events, such as episodes of increased symptoms or increased airflow limitation, have been identified as mild exacerbations in some studies.<sup>89,268</sup> These episodes tend to be responsive to short-acting  $\beta_2$  agonists prescribed for relief and are prevented by long-acting  $\beta_2$  agonists, whereas events leading to the prescription of oral corticosteroids or hospital admission are less responsive,<sup>89,188</sup> suggesting important differences in pathogenesis. Evidence<sup>269</sup> suggests that more severe events (ie, those resulting in unscheduled medical attention or unscheduled use of oral corticosteroids) are associated with loss of bronchodilator responsiveness and the presence of airway inflammation. Events defined in this way have proved to be a robust outcome measure and are highly responsive to anti-inflammatory treatment. However, yet again objective biomarkers of different inflammatory patterns associated with deteriorations and of recovery are needed, rather than outdated, subjective approaches.

One consequence of not clearly discriminating between loss of symptom control and genuine attacks has been that the inadequate word exacerbation is often used to describe acute asthma attacks. This term has fostered the assumption that these attacks are mildly inconvenient and readily reversible, rather than being a marker of a high risk of future attacks and even death. In the context of many airway diseases, this perception is an absolute travesty. COPD and asthma lung attacks are responsible for up to 10% of acute medical hospital admissions in the UK and COPD lung attacks have mortality rates and costs comparable with those of heart attacks.<sup>270</sup> Lung attacks in patients with cystic fibrosis are associated with more rapid decline in lung function and increased risk of death or lung transplantation.<sup>271</sup> Repeated asthma attacks are also associated with a more rapid decline in lung function. In a post hoc analysis of the START study,<sup>272</sup> in children and adults, but notably not adolescents, an accelerated decline in spirometry was observed in individuals who experienced an asthma lung attack while on placebo, but not on budesonide. The protective effect of budesonide suggests that something can be done to prevent this accelerated decline in lung function. Whether the exacerbations observed were associated with poor adherence or the intrinsic severity of the disease is irrelevant to the question of whether lung attack is a useful term. The term exacerbation does not describe a temporary inconvenience, but a sign of a worse prognosis, which requires immediate action.

An additional problem with regard to the dissociation between symptoms or disordered airway function and the risk of asthma attacks is that an asymptomatic patient with normal lung function cannot be assumed to be free of risk.<sup>189</sup> Monitoring algorithms and asthma treatment goals will have to change in response to this new understanding. Despite an increasing

understanding of risk factors for attacks, and the availability of biomarkers that provide a better perspective on preventable risk than is available from a symptom and physiology-based assessment, risk stratification is not a part of routine clinical practice.<sup>272</sup> The recent UK national enquiry<sup>86</sup> into asthma deaths identified, once again, that apparently low-risk patients continue to die of asthma. New management algorithms are needed that are applicable in non-specialist care, which include a clear assessment and quantification of risk of attacks and likely benefit of treatment, such as that outlined previously. These assessments need to move beyond the airway, to extrapulmonary and environmental and lifestyle factors.<sup>129</sup> We need to establish whether this approach helps patients make a decision about committing to long-term treatment and health-care providers a decision about making this treatment available and affordable.

The clinical response to acute attacks is largely standardised and based on a one-dimensional severity assessment, despite increasing evidence that these episodes are just as heterogeneous as stable airway disease.<sup>273,274</sup> The acute attack provides a unique opportunity to offer a thorough overall assessment of the circumstances of the attack in a captive and potentially more receptive patient. Are we making the most of this opportunity? Patients admitted to hospital with an acute attack have a poor prognosis and often require additional treatment, particularly in the short term.<sup>275</sup> Could more be done to prevent this happening? An initial step might be an end to the prescription of a fixed-term dose of oral corticosteroids with no follow-up to assess response. Additionally, treatment protocols should mandate a re-assessment of all aspects of care to identify the following: what went wrong and could it have been prevented, was the response correct in terms of the treatment plan, and should the treatment plan be altered with the wisdom of hindsight?

An even greater problem exists regarding wheeze attacks in children between birth and age 5 years. Conflicting evidence exists about whether either corticosteroids<sup>276–278</sup> or leukotriene receptor antagonist therapy<sup>279</sup> reduce the risk of attacks or are useful in the treatment of attacks.<sup>210,280</sup> Effective therapies are urgently required in this age group.

### Where do we want to go?

The poor response of the respiratory community to exacerbation is in stark contrast to the cardiologists' focused, highly effective, and life changing response to a heart attack. Respiratory health-care providers should emulate cardiologists as follows: first, a lung attack is not a temporary inconvenience—it can be associated with permanent damage and is a sign of a worse outlook (including risk of death) unless something is done—and patients and families need to know this; second, a lung attack should prompt a full review of all aspects of

the problem, including comorbidities, management, adherence, adverse environmental factors and psychosocial issues, which must not be permitted to decline into a box-ticking exercise; third, clinicians must make the most of opportunities to prevent these episodes. In many countries, high-risk periods for asthma attacks have been identified, including the period in which children return to school in the autumn, thunderstorms in early summer, and the winter respiratory virus season. Attacks during these periods are most commonly driven by inflammation and therefore, might be readily preventable with regular or as-required inhaled corticosteroids<sup>198</sup> or biological drugs.<sup>254</sup> Parents and children should be aware that taking their preventer inhalers is just as much a part of preparing for a new school year as buying new school shoes or a new uniform; fourth, the meaning and consequences of an asthma attack must be communicated more effectively to patients and other stakeholders. The assessment of risk of a recurrent lung attack should be as much a part of the routine management of airway disease as it is in cardiac disease.

More could be done to understand the heterogeneity of asthma attacks at all ages, and the basis of wheeze attacks in children between birth and age 5 years. Viral infection is assumed to be the inevitable trigger, but bacteria are frequently isolated<sup>165</sup> (although whether cause or consequence is not easy to determine), and subgroups of patients who should be treated with antibiotics without corticosteroids need to be identified. Studies in patients with COPD who have lung attacks show that patients who present in a similar way can have considerably different patterns of airway inflammation.<sup>281</sup> Increasing evidence<sup>282,283</sup> suggests that this heterogeneity can be defined using readily accessible biomarkers, such as the peripheral blood eosinophil count, and that this information allows management to be individualised, resulting in more economical use of treatment and potentially better outcomes. Importantly, inflammatory patterns of attacks are repeatable within adult patients and can be predicted from findings when stable.<sup>281</sup> The treatable traits approach to the treatment of stable airways disease discussed previously could therefore be just as applicable in patients presenting during an acute attack, and in planning the best approach to prevention of a recurrence.

Whether specific biological treatments have a role in treatment and secondary prevention of attacks, at least in adults presents an interesting question. The interleukin-5 receptor blocker benralizumab has a rapid and very complete suppressive effect on blood eosinophil count<sup>284</sup> suggesting that it might have utility as an alternative to prednisolone treatment in patients with eosinophilic exacerbations. Evidence already exists indicating that treatment reduces the rate of relapse in patients presenting with an attack.<sup>285</sup> The administration of an injected, long-lasting anti-inflammatory drug might have

advantages in a situation in which treatment adherence is not always assured.

Prevention strategies need to move on from tertiary to secondary prevention of attacks. Simple, readily collectable variables, such as previous attack or emergency room attendance, high  $\beta_2$ -agonist consumption, a high short-acting  $\beta_2$  agonist to inhaled corticosteroids prescription ratio, poor symptom control, impaired lung function, and raised markers of eosinophilic airway inflammation could form part of a primary prevention strategy and could be built into a routine, at least annual, review.<sup>272</sup> Such a review could result in a risk score, similar to cardiovascular risk assessment, and an individualised recommendation for reducing risk. Such an approach might reap the same sorts of benefits currently enjoyed in cardiovascular medicine.

## Getting serious about severe disease

### Where are we now?

The UK national report on asthma deaths<sup>86</sup> stated that 60% of asthma deaths were in patients with mild or moderate asthma. These findings suggest that our definitions of severe asthma must be wrong, because it is difficult to think of a worse outcome than death. The conventional definition of severe asthma is of symptoms and poor lung function or exacerbations (used interchangeably) despite the prescription of high-dose anti-inflammatory and bronchodilator therapy.<sup>286</sup> This subset of patients (about 20% of all patients with asthma) are referred to as having difficult to treat or difficult asthma. In many patients, after detailed systematic evaluation, a coexistent problem is identified (tables 5, 6), either alone (misdiagnosis) or together with mild or moderate asthma, and when effectively managed, symptoms can be controlled.<sup>287</sup> However, in practice often very little is done beyond asking the patient if they are taking treatment. The biggest problem doctors avoid discussing is adherence, an important factor even in those referred to tertiary level severe asthma centres.<sup>288</sup> A protocol-driven adherence assessment that is readily available would minimise the risk of committing a patient to long-term expensive biological treatment when their disease is readily controllable with inhaled treatments—eg, modification of medication delivery devices.

Some patients within this wider difficult asthma group have severe asthma, which cannot be controlled with available treatments, and in whom alternative diagnoses have been excluded, adherence with treatment has been checked, comorbidities have been treated, and trigger factors have been removed. The current definition of severe asthma requires high-dose treatment (high-dose inhaled corticosteroids plus a second controller used for the previous year or systemic corticosteroids  $\geq 50\%$  of the previous year) to either maintain asthma control or which fails to achieve control (panel 7).<sup>286</sup> Severe asthma represents a

considerable unmet medical need and is the subject of intense mechanistic and therapeutic study, which needs to be transferred to the clinic. Novel therapeutics, which target a particular phenotype of severe asthma (severe eosinophilic asthma), have been introduced in the clinic and will substantially increase management options for this group of patients. Precise clinical assessment, with a focus on inhaled corticosteroids adherence, is crucial to ensure these therapies are used in the correct patient group. The arrival of these therapies will allow the research focus to shift towards understanding non-eosinophilic mechanisms in severe asthma, whereby substantial ignorance remains despite the therapeutic need. Ultimately, in all the asthmas, pathway defined approaches and treatments are required.

### Where do we want to go?

#### A better definition of severe asthma

Difficult asthma is not a diagnosis but an umbrella term to describe a clinical problem, which requires careful multidisciplinary assessment. The definition must be modified to include a component of risk, focusing not only on airway phenotype, but also extrapulmonary comorbidities and social and environmental factors. The first and most important challenge is to establish a definition that includes risk assessment and reflects clinical reality. The 2014 European Respiratory Society and American Thoracic Society taskforce definition<sup>286</sup> (panel 7) recognised that different criteria can be used to define severe asthma and does not assume that these criteria are pathogenically similar. The Commissioners propose a new definition of severe asthma, which develops this important conceptual shift and focuses more explicitly on the risk of attacks (panel 8).

Clearly a definition on its own achieves nothing; what this new definition should achieve is a detailed and focused response that assesses all aspects of the patient's airway disease, and the treatment plan, rather than assuming that an asthma attack is a minor inconvenience. Another unmet clinical need is a detailed and agreed assessment plan. After such an assessment, with good basic management in some patients the disease might no longer be severe and risk might be greatly reduced. However, short-term improvement might be followed by long-term recidivism, and ongoing efforts to support better management are essential.

#### Tackling poor treatment adherence

The challenge of non-adherence for maintenance treatment exists in all chronic diseases and is also prevalent in difficult asthma.<sup>288</sup> The field of respiratory medicine has been slow to embrace modern technologies to assess adherence. An electronic prescription record is easy to obtain but is not always done; if no prescriptions are being collected, the patient is not taking their medication. The next step, used in

#### Panel 7: European Respiratory Society and American Thoracic Society 2014 definition of severe asthma<sup>286</sup>

##### Definition of severe asthma for patients aged 6 years and older

Asthma that required treatment with medications suggested by guidelines for Global Initiative for Asthma stages 4–5 asthma (high-dose inhaled corticosteroids\* and long-acting β<sub>2</sub> agonists or leukotriene modifier or theophylline) for the previous year or systemic corticosteroids for 50% or more of the previous year to prevent the disease from becoming uncontrolled, or asthma that remains uncontrolled despite this therapy

##### Uncontrolled asthma defined as at least one of the following:

###### Poor symptom control

Asthma Control Questionnaire score consistently higher than 1·5, asthma control test score of 19 or less (or defined as not well controlled by the National Asthma Education and Prevention Program or Global Initiative for Asthma guidelines)

###### Frequent severe exacerbations

Two or more courses of systemic corticosteroids (>3 days each) in the previous year

###### Serious exacerbations

Admission to hospital at least once, intensive care unit stay, or mechanical ventilation in the previous year

###### Airflow limitation

Airflow limitation after withholding appropriate bronchodilator with a forced expiratory volume in 1 s less than 80% predicted (with reduced forced expiratory volume in 1 s to forced vital capacity ratio defined as less than the lower limit of normal)

##### Controlled asthma that worsens on tapering of these high doses of inhaled corticosteroids or systemic corticosteroids (or additional biological drugs)

\*The definition of high-dose inhaled corticosteroids is age-specific.

some centres, is the use of a microchip to monitor when the device (eg, an inhaler) is being activated.<sup>289</sup> However, this does not indicate whether the patient is inhaling the drug correctly. Thus, a need exists for a device that detects an adequate inhalation, has a real-time alarm for the patient if a dose is omitted, and has a real-time alarm for the physician if for example, three doses are omitted or rolling cumulative adherence drops below 80%, or in the case of short-acting β<sub>2</sub> agonists, more than a set number of doses are taken in a particular timeframe. A mandate, supported by health-care payers, should ensure that all inhaled medications are dispensed in such a device.

Biomarker-based assessments of corticosteroid response might identify patients who should achieve good asthma control with better adherence to standard treatment and without escalation to some of the novel expensive parenteral biological therapies.<sup>290</sup> Assessments of this type must replace the treatment trial approach used for this subgroup of patients. Key challenges going forward will be to ensure widespread implementation of strategies to identify and manage non-adherence effectively in this patient group.

#### A better understanding of the role of comorbid conditions

Many comorbidities are commonly reported in a population with severe asthma (tables 5, 6) and

**Panel 8: Definition for severe asthma as proposed by the Commissioners**

- One severe asthma attack in individuals of all ages should be considered evidence of severe disease, and trigger a detailed evaluation of the disease
- Spirometry persistently below the normal range despite moderate doses of inhaled corticosteroids and one other controller
- Persistent variable airflow obstruction despite prescription of a long-acting  $\beta_2$  agonists and inhaled corticosteroid combination
- Evidence of persistent airway eosinophilia (in adults) despite the prescription of a moderate dose of inhaled corticosteroid; however, symptoms without evidence of airway eosinophilia, airway dysfunction, and no history of exacerbations should not qualify as severe disease
- Adverse factors in the behavioural or environmental domain, including unscheduled visits, failure to attend appointments, poor adherence, smoking, allergenic environment, and the three Ds—denial, depression, and disorganisation

management guidelines advocate identification and management of these conditions. However, the evidence that managing these comorbidities has a major clinical effect on asthma outcome in this population is scarce. Despite substantial literature discussing the association between gastro-oesophageal reflux and asthma, causality has not been established, and although common in all severities of asthma including difficult asthma, the effects of acid suppression therapy have been disappointing.<sup>291</sup> These results might be observed because non-acid reflux is still occurring or because the presence of gastro-oesophageal reflux has little effect on underlying asthma but triggers cough perceived as asthma, either because asthma causes reflux,  $\beta_2$  agonists increase reflux, or reflux is a harmless side-effect. Gastro-oesophageal reflux can be effectively treated with fundoplication and efficacy has been suggested in asthma.<sup>292</sup> However, a sham-controlled fundoplication study has never been done although this type of study is feasible and has been useful in assessing established surgical practice in other disease areas.

The precise link between obesity and severe asthma remains unclear; however, discrete obese phenotypes have emerged consistently in cluster analyses of severe asthma cohorts.<sup>25,293</sup> A number of biologically plausible interactions have been suggested, including corticosteroid insensitivity, mechanical forces involved in ventilation, hormonal influences (such as leptin and adiponectin) and other comorbidities, such as gastro-oesophageal reflux and metabolic dysfunction.<sup>126</sup> However, the benefits of weight-loss reduction programmes and bariatric surgery, although encouraging, remain unclear.<sup>294,295</sup> A challenge for the

future will be to differentiate between association and cause and effect for all commonly reported comorbidities in severe asthma, which will enable better targeting of interventions, including invasive surgical procedures, in this patient group.

**Precision biomarker directed medicine in severe asthma**

Data<sup>10,25</sup> in adult patients with severe asthma, suggest considerable heterogeneity of airway inflammation exists. Between 25% and 50% of patients have a prototypic type 2 inflammatory cell or cytokine gene signature despite presumed adherence with high-dose corticosteroid treatment.<sup>10,25</sup> In patients with severe asthma with no evidence of type 2 inflammation, their corticosteroid dose is likely to have been escalated inappropriately in an attempt to manage persistent symptoms that are not corticosteroid responsive.<sup>10</sup> In view of the evidence that corticosteroid responsiveness is confined to type 2 disease,<sup>6,296</sup> a key challenge for the management of severe asthma in the future is to develop objective tests and validated management algorithms to not only initiate corticosteroid treatment, but also to allow clinicians to determine that additional corticosteroid treatment will not produce any further clinical response. Adjustment of corticosteroid treatment using sputum eosinophil count has shown benefit in terms of exacerbation reduction in adults,<sup>10,11</sup> but repeated sputum analysis has been challenging to deliver in routine clinical care, and the results are variable in children.<sup>297</sup> Moving away from the symptom driven escalation of corticosteroid treatment that is advocated, particularly in patients with severe asthma, will be a major component of delivering precision treatment in severe asthma in the future and will facilitate optimisation of corticosteroid dose. This shift would also allow a diagnosis of severe asthma to be made without escalation of corticosteroid treatment past the point in which in many patients any therapeutic benefit is unlikely.

Some patients with type 2-high disease have refractory eosinophilic asthma, whereby despite adherence with high-dose inhaled corticosteroids, persistent type 2 cytokine driven inflammation and airway eosinophilia occurs. These patients (around 3% of the total population with asthma) frequently require regular or frequent courses of systemic corticosteroids to improve disease control. These patients develop well-recognised side-effects, including osteoporosis, diabetes, hypertension, cataracts, psychological disturbance, Cushingoid features, and airway and systemic infections.<sup>298,299</sup> The therapeutic management of this group of patients with severe asthma will be transformed over the next decade with the advent of additional novel target specific therapies targeting the type 2 cytokine axis.

Omalizumab has been available in the clinic since the early 2000s. Clinical trials have shown a reduced number of unscheduled emergency visits and hospital admissions in patients treated with omalizumab compared with those given a placebo,<sup>300</sup> and current guidelines advocate

the use of omalizumab as an add-on therapy in severe asthma.<sup>286</sup> However, the fact that serum IgE is not a useful biomarker of treatment response<sup>111</sup> is problematic, and thus non-specific clinical measures of asthma severity are used to guide prescription decisions.<sup>111</sup> The risks and benefits of biological drugs must be assessed objectively by biomarkers that are demonstrably and plausibly linked to the targeted biological process (ie, FeNO for omalizumab<sup>111</sup>). Otherwise, an unacceptable and inefficient reliance will be placed on treatment trials in individual patients.

New biological therapies that target interleukin 5 are now available for use and other biological drugs targeting type 2-high disease will potentially be available in the next 5 years (table 3). The development of new therapies will generate many interesting questions, including differential efficacy between monoclonal antibodies targeting interleukin 5 (mepolizumab and reslizumab), the interleukin-5 receptor (benralizumab), interleukin-13 (lebrikizumab and tralokinumab) and interleukin-4 receptor  $\alpha$  (dupilumab). Other strategies that inhibit the type 2 inflammatory axis, including orally active prostaglandin D2 receptor 2 antagonists (fevipiprant)<sup>301</sup> and anti-thymic stromal lymphopoietin,<sup>302</sup> will also be targeting overlapping patient groups. Identifying which patients respond better to different classes of drugs might require head-to-head studies, which are unlikely to be funded by the pharmaceutical industry. Many of these new therapies will come to market with a companion diagnostic or predictive biomarker of clinical response. Before release, clinical trial data should be made open access and individual patient biomarker data analysed independently with the aim of identifying biomarker signatures predictive of treatment efficacy. Patient organisations and health-care providers should lobby the pharmaceutical industry to ensure this happens.

Evidence suggests that different biomarkers identify different aspects of type 2 mediated inflammation (tables 1, 3). Both elevated blood eosinophilia counts and FeNO concentrations are associated with the risk of severe asthma attacks but a greater risk is evident if both are elevated.<sup>107</sup> Existing data show differences in the ability of biomarkers to predict treatment responsiveness. FeNO and serum periostin are good biomarkers of treatment response to biological drugs that inhibit interleukin 13 in adults with severe asthma,<sup>31</sup> whereas the blood eosinophil count is most closely associated with a response to anti-interleukin 5<sup>12</sup> (table 3). Moreover, treatment with anti-interleukin 5 reduces the blood eosinophil count but not FeNO,<sup>12,28</sup> whereas the opposite occurs for anti-interleukin 13.<sup>31</sup> Therefore, biomarker profiles could possibly be used to identify subgroups of patients within the type 2-high population who have different risks of attack and are particularly suited to different cytokine blockade. Whether post-hoc analysis of existing research databases is sufficient to identify these

relationships is uncertain. Prospective information will be important and we suggest that biological drugs should only be prescribed in tertiary centres after a protocol driven assessment of why the patient is not responding to standard therapy, and should be subjected to a protocol driven therapeutic trial, with collection of clinical and preferably biological data in a standardised manner whereby the information collated is made available via a public database. More information is needed on treatment of severe childhood asthma.

All biological drugs that target type 2 cytokines have a larger effect on the risk of future attacks than on ongoing symptoms and lung function impairment (table 3). These drugs are also likely to be expensive so health-care payers will want treatment efficacy decisions to be made early. This presents challenges as short-term changes in symptom scores and lung function are unlikely to be large enough on an individual basis to be useful as a predictor of long-term efficacy, particularly as interpretation of changes will be confounded by a strong tendency for regression to the mean. Additionally, this might not represent a valid approach because the mechanism of short-term improvement in symptoms and long-term reduction in exacerbations differ. We suspect that treatment decisions will, for the first time in airways disease, need to be made on the basis of measures of the relevant pathological pathway. Longer-term treatment goals could be set, and failure to achieve these should prompt a re-evaluation of the importance of that trait and a consideration of alternative treatable traits.

Bronchial thermoplasty delivers radiofrequency energy to the airways with the aim of reducing airway smooth muscle mass and hyper-responsiveness. The utility of thermoplasty in the management of severe asthma remains to be established. No data from existing clinical trials indicate that response is linked to a particular pathophysiological abnormality, or trait<sup>303,304</sup> (table 4). Thermoplasty treatment is thought to reduce airway smooth muscle responsiveness, but such an effect has not been shown consistently, nor has increased baseline airway responsiveness been linked to treatment efficacy. Whether new imaging and physiological techniques, which have been used to identify focal areas of acute airway narrowing,<sup>305</sup> will also delineate focal areas particularly suited for targeted treatment, and whether such an approach leads to better outcomes, are important research questions for the future.

Asthma symptoms and altered physiology often manifest in the absence of type 2 inflammation, but little information is available about which underlying pathophysiological mechanisms drive these processes. Possibilities include abnormal perception of symptoms, a different inflammatory process, non-inflammatory structural problems such as abnormal smooth muscle contractility, aberrant epithelial signalling, or airway

infection.<sup>150</sup> Additionally, research<sup>126</sup> has highlighted the association between systemic inflammation, especially systemic interleukin-6 inflammation and outcomes of severe asthma, and has indicated that inflammatory mechanisms that arise outside the lung might cause lung injury. These mechanisms might be associated with the inflammation that occurs with ageing and increasing bodyweight. Such mechanisms include inflammation associated with metabolic dysfunction, including interleukin-6 pathways and pathways associated with insulin resistance.<sup>126</sup> Importantly, some of these pathways are tractable in terms of treatment.

The greatest future challenge in severe asthma remains disease-modifying therapy and cure. Understanding why patients with a pattern of disease (type 2-high), which is usually responsive to low doses of inhaled corticosteroids, become relatively corticosteroid resistant and require high-dose (often systemic) treatment, might enable the disease to be targeted therapeutically. This area has been the subject of study for many years, but no precise mechanism, evidenced by the absence of a proven therapeutic, has emerged.

## Improvement of research

### Clinical trials

Since the 1990s, clinical research has been characterised by randomised controlled trials of moderate and severe asthma, in populations poorly generalisable to asthma patients in clinical practice,<sup>179</sup> without characterisation of phenotypic subgroups, and inadequate consideration of other treatable traits associated with overlapping disorders, comorbidities, and lifestyle or environmental factors. Progress could have also been delayed by the pharmaceutical industry setting the agenda primarily to fulfil regulatory requirements for licensing a new therapy, and with the exception of the monoclonal antibody studies, an undue emphasis on me-too trials of inhaled corticosteroids and long-acting  $\beta_2$  agonist medications. The focus on moderate and severe asthma in trials based primarily in tertiary hospital research institutions, has resulted in little available evidence for the management of children or adults with so-called intermittent or mild disease, who experience substantial yet largely unrecognised morbidity. Clinical research needs to encompass the spectrum of disease severity and this will require greater utilisation of primary care-based research centres. However, the onus will then be on primary care centres to improve diagnosis and monitoring of airway disease in their patients, and (not just in primary care) to ensure that patients actually have an airway disease (the nature of which is known) and are taking conventional medications appropriately before a new therapy is trialled. Considerable untapped potential exists for asthma research in primary care, which uses electronic medical records containing clinical, laboratory, and health utilisation outcome data. Encouragingly, this opportunity is being exploited

effectively in the Salford Lung Study<sup>306</sup> and by the Research Effectiveness Group.<sup>307</sup>

Research also needs to encompass the spectrum of ages in which asthma occurs, including infants (aged 0–5 years) and children aged between 5 and 16 years, in whom few clinical trials have been done, yet paradoxically, a high burden of disease exists. For similar reasons, resourcing also needs to be provided to ensure more randomised controlled trials are done in low-income and middle-income countries, as well as high-income countries, and that medications are affordably priced for low-income and middle-income countries. The European Asthma Research and Innovation Partnership published an excellent report<sup>308</sup> that emphasised the need for a collaborative approach to future research in asthma and highlighted areas of particular need. This work provides a solid framework for improving the quality of research and, ultimately, asthma outcomes.

External validity of evidence from randomised controlled trials is crucial to establish whether the findings inform the likely benefits and risks of a proposed treatment to individual patients. The traditional requirements of major randomised controlled trials, which mandate that participants have marked bronchodilator reversibility, short smoking histories, and designated symptom reliever use, or lung function parameters have resulted in good internal validity, but poor generalisability of the findings to clinical practice. The clinical relevance of this is illustrated by the observation that most (>90%) adult patients with an asthma diagnosis in the community would not have been eligible for inclusion in the major randomised controlled trials that have informed guidelines, on which recommendations for their management have been made.<sup>179</sup> The requirement for bronchodilator reversibility for participation in clinical trials has meant that the benefits of long-acting bronchodilators might have been overestimated. Because evidence of active eosinophilic airway inflammation was not a prerequisite for patient enrolment in the clinical trials that have informed guidelines, the benefits of inhaled corticosteroids and other more specific inhibitors of this process might have been diluted and thus underestimated.

The Commissioners postulate that features such as bronchodilator responsiveness, severity of asthma, diagnostic label, level of control, health-care utilisation, and smoking history should not be inclusion or exclusion criteria, but rather key covariates and potential predictors of response with the study powered for subgroup analysis. These predictors would supplement the use of biomarkers of type-2 disease, which already have established utility as predictors of response to inhaled corticosteroids and monoclonal antibody therapy directed against associated cytokines. In this way, the findings from randomised controlled trials will not only be more generalisable to patients with asthma managed in clinical practice, but will also enable

identification of subgroups with a preferential response to treatment, or a higher risk of adverse responses. Initial randomised controlled trials of broad populations could be followed by randomised controlled trials in highly characterised groups whose response to intervention is different in a clinically significant way. Focused randomised controlled trials would also be applicable early on when the treatment target and its association with disease expression are well known. This approach will ensure that the findings have high external validity to such specific phenotypic groups, which would aid the development of the precision approach to management outlined previously. Table 4 provides information about the target population, potential covariates, and most rational outcome measures for established treatable traits.

Although standard outcome variables such as lung function, composite measures of asthma control, and health-care utilisation provide a multidimensional assessment of efficacy and risk, these variables might be inadequate alone if a comprehensive assessment of efficacy and safety is to be obtained. This inadequacy is illustrated in the differing interpretation of the large randomised controlled trials of the single inhaled corticosteroid and long-acting  $\beta_2$  agonist maintenance and reliever therapy regimen, in which the absence of objective measures of medication use contributed to difficulty in assessing key outcomes such as  $\beta$ -agonist overuse, delay in seeking medical help during asthma attacks, and systemic corticosteroid exposure.<sup>193</sup> A highly rigorous, randomised controlled trial<sup>109</sup> in high-risk asthma subsequently showed the potential of electronic monitoring of medication use to objectively measure such clinical features of a therapeutic regimen. This study not only showed the favourable efficacy and safety profile of this single inhaled corticosteroid, and long-acting  $\beta_2$ -agonist maintenance and reliever therapy regimen in high-risk asthma, but also set a new benchmark for randomised controlled trials in which patterns of medication use are electronically recorded.

A greater emphasis is needed on the investigation of the treatment of overlapping disorders, comorbidities, and environmental and lifestyle factors that contribute to the burden of disease in asthma. This approach recognises that asthma is a complex disease and that an evidence base for the recognition and treatment of these potentially treatable components might not only improve outcomes, but also move the field towards precision medicine in asthma.

#### **Integration of epidemiology, genetics, and translational research**

Many observational, cross-sectional, and longitudinal studies have been performed in which detailed clinical descriptions of affected patients are absent; the basic science has been outstanding but the clinical characterisation scarce. One of the main challenges for

understanding the epidemiology and genetics of asthma is the absence of a consensus for defining the disease, which is partly a consequence of the underlying heterogeneity. Unless epidemiological and genetic studies find better ways to distinguish between different diseases under the umbrella diagnosis of asthma at the population level, establishing the unique underlying genetic risk factors of the diseases, or identifying novel therapeutic targets for stratified treatment will be impossible, because any signal will be diluted by phenotypic heterogeneity.<sup>310</sup> This heterogeneity might result in discrepancies between different studies that estimate asthma prevalence and associated risk factors. For example, a 2010 review<sup>311</sup> showed that in 122 epidemiological publications investigating risk factors for childhood asthma, no fewer than 60 different definitions of asthma were used. However, the application of the four most commonly used asthma criteria to a high-risk population of children resulted in the overall agreement of only 61%, suggesting that 39% of study participants might move from being considered asthma cases to non-asthmatic controls, depending on which definition was used.<sup>311</sup> The overall effect of such heterogeneity on reported associations with environmental or genetic risk factors is unclear, but should not be underestimated. Few epidemiological or genetic studies have characterised subjects affected by wheeze, cough, and asthma in clinical settings by detailed measurement of the traits discussed previously (table 4). The reluctance of epidemiologists, clinicians, geneticists, immunologists, and numerous other specialties to participate in cross-disciplinary collaborations in the field of asthma has caused divisions within the clinical community and led to rigid approaches.

In view of the functional interdependencies between the molecular components in a human cell and mechanical characteristics of the lung, asthma is rarely a consequence of an abnormality in a single gene, a single environmental factor, or a single functional abnormality of the lung. Asthma reflects the system behaviour induced by environmental perturbations of the complex intracellular and intercellular network that links genes, cells, tissue, and organ networks. Novel epidemiological, bioinformatics, and machine learning tools offer innovative options to explore the systemic complex interplay between molecular and functional mechanisms of a particular disease, leading to the identification of disease modules and pathways, but also the molecular relationships between apparently distinct endotypes or phenotypes.<sup>312</sup>

Although the complexity of the scientific world is ever increasing and specialties are struggling to keep up with the exponential rise of information and data, reflection on the overarching general concepts of disease inception has been neglected. Epidemiological attempts to isolate a few determinants from numerous

confounding factors are not adequate to define a complex asthma syndrome. No novel treatment will resolve the global asthma epidemic. The clinical community rarely appreciates that different biological pathways account for the clinical features termed asthma, which are not necessarily reproducible in other environmental and ethnic contexts—eg, different genes for asthma have been found in different ethnic groups in genetic studies.<sup>313</sup>

Genetic research has addressed the hereditary component of asthma (usually defined as parentally or patient-reported doctor-diagnosed asthma) in multiple large genome-wide association studies.<sup>314–318</sup> Although heritability estimates suggest that about half of the risk variation is attributable to genetic factors,<sup>314</sup> genome-wide association studies have identified only a few common variants accounting for only a small part of asthma risk.<sup>315</sup> For example, the odds ratio for the major genetic locus 17q12-21, which has been widely replicated, amounts to less than 1·5. Additionally, the population attributable risk fraction for the joint action of all significant loci of the GABRIEL genome-wide association studies<sup>315</sup> accounted for only 38% of childhood onset asthma cases. In addition to the genome-wide association studies initiatives, a wide array of candidate genes, all with weak effects, have been identified.<sup>316</sup> Notably, when a much more precise and specific definition was used (early-life onset asthma with recurrent, severe exacerbations in children younger than 5 years), genome-wide association studies have identified associations with a much greater effect size, and novel susceptibility genes such as *CDHR3* (coding single nucleotide polymorphism rs6967330, C529Y).<sup>317</sup> Subsequent studies have shown that *CDHR3* expression facilitates rhinovirus-C binding and replication, and that a genetic variant which was linked with hospital admissions for early-onset childhood asthma in birth cohort studies mediates enhanced rhinovirus-C binding and replication,<sup>318</sup> providing further indirect evidence that the use of problematic umbrella terms should be avoided in epidemiology and genetic studies. This sort of triangulated approach will be important in future genetic and epidemiological studies.

Similarly, most of the known environmental risk factors for asthma also have weak effects,<sup>319</sup> as discussed previously. Numerous environmental exposures are important in the aetiology and severity of asthma, but the effect of environmental factors differs between individuals with different genetic predispositions. However, the precise nature of these complex associations remains unclear. One of the most replicated examples of gene–environment interactions is that between endotoxin exposure and variants of the *CD14* gene. Several studies<sup>320</sup> have confirmed that high endotoxin exposure is protective against allergic sensitisation, but only among individuals with a specific genotype (C allele homozygotes of *CD14*-159, rs2569190), and not in individuals with other genetic variants. The interactions

between genotype and other environmental exposures (eg, dust mite exposure) add further complexity, resulting in a complex gene–environment interaction.<sup>73</sup> Further examples include the observation that the same environmental exposure might have opposite effects on asthma among individuals with different genetic predisposition (eg, the effect of early-life day care attendance on asthma development is opposite in children with different variants in the *TLR2* gene, with day care being protective in some, but increasing the risk in others).<sup>321</sup> Thus, in intervention studies (including primary prevention), when identifying environmental protective and susceptibility factors that are amenable to intervention, individual genetic predisposition should be considered to enable the development of personalised strategies.<sup>322</sup> Therefore, not only the treatment but also prevention will have to be stratified.

Another issue often neglected is that the effects often attributed to environmental exposures might actually reflect genetic predisposition (gene–environment association). For example, the association between antibiotic use and childhood asthma (which is often attributed to antibiotics changing the host microbiome), might arise as a result of confounding, in which impaired antiviral immunity and increased susceptibility to viral infections increases the likelihood of both early-life antibiotic prescription and asthma in later life, with both asthma and early-life antibiotic prescription being associated with the same genetic variants on 17q21.<sup>57</sup>

The transfer of knowledge from asthma epidemiology studies to effective public health or pharmacological interventions for the primary prevention of asthma has been disappointing. Potential intervention strategies will need to be feasible for implementation either as universal public health measures, or strategies targeted to specific phenotypes, including but not limited to infants at high risk of developing asthma. The need for interventions to be easily introduced and taken up at the community level would enhance both participation in the research and subsequent implementation if proven effective. This requirement is highlighted by the difficulties of studies that have investigated multifaceted allergen avoidance, dietary, and tobacco smoke avoidance strategies,<sup>323</sup> from which it is not possible to determine which interventions contributed to the effects shown, or even whether components of the intervention might have individually made matters worse. For example, allergen avoidance strategies might have moved some individuals from high tolerance to the sensitisation range. This concern, together with the expensive and burdensome nature of the interventions has restricted their potential implementation as public health programmes. Difficulties are also apparent with the strategies for some of the novel risk factors not yet subject to interventional studies. An example is the widespread use of high doses of inhaled short-acting  $\beta_2$  agonists for episodes of wheezing in infancy and

whether this treatment might increase the risk of established asthma in childhood. This hypothesis is based on the observation that inhaled short-acting  $\beta_2$ -agonist therapy increases airway hyper-responsiveness in both children and adults<sup>324,325</sup> and can do so within weeks. However, major practical barriers would be encountered if such a study was attempted, or practice needed to change as a result of such a study, because any restriction in  $\beta$ -agonist use contradicts current principles in terms of the treatment of wheeze in infancy.

In addition to feasibility issues, other limitations of intervention studies include small sample sizes, highly selected populations, difficulty in masking interventions, losses to follow-up, and the paucity of reporting long-term outcomes. An unavoidable lag would exist between starting and completing the study, without the opportunity to add additional interventions on the basis of new knowledge. To make progress, studies of interventions that potentially modify the risk of asthma will require a series of large-scale multicentre studies involving international collaborations, to enable the recruitment of enough participants to allow adequate power for small effects to be established in different populations. An intervention that had even a relatively small effect on the development of asthma or its severity would be of major importance for public health.

An innovative combination of trial design and statistical methods might be required to overcome the main limitations associated with conventional randomised controlled trials. Such an innovative approach would be a randomised platform trial which uses Bayesian statistical methods from the outset, planned trial adaptations, including response adaptive randomisation, and the evaluation, in parallel and in sequence, of multiple interventions including the evaluation of interactions between interventions.<sup>326</sup> Relevant subgroups could be identified from the outset, with the analysis allowing for the probability of differential treatment effects in these defined subgroups. Biological traits that underpin the heterogeneity of asthma could be used, rather than measuring ill-defined and heterogeneous common endpoints, and the use of biomarkers that might identify a beneficial effect early in the disease course would be an advantage. Although such a methodological approach is in its infancy, the principles on which it is based have the potential to achieve substantive gains in trial efficiency, allowing multiple research questions to be answered within a single randomised controlled trial. Such an approach would also enable the study of additional novel interventions identified during the study, which is important as the duration of such studies is likely to be more than 10 years.

#### **Animal models and basic immunology**

Although progress has been made in animal models and basic immunology, such advances have been incremental rather than practice changing and adequate models in

key areas remain scarce. Animal models do not adequately reflect the distinct clinical phenotypes and endotypes of human disease described previously. Most models use mice and focus on T-helper-2 phenotypes with high eosinophilia and a type 2 cytokine profile. No models that clinically cross-validate models of non-type 2 phenotypes are available. For example, no models represent neutrophilic asthma, and no models adequately reflect steroid resistant phenotypes. The biology of neutrophilia is, however, very well understood, particularly in pulmonary infection models, but few translational studies have been done. Models of other clinically important phenotypes are also poorly addressed. An almost exclusive emphasis is placed on the acute phase of the host response to aeroallergens, and although more focus on how to promote resolution of injury is needed, very few chronic exposure models exist. Genetic models of chronicity need to be cross-validated against human endotypes.

An excessive focus is placed on the mouse as an experimental species, although pathology in mice and humans varies considerably.<sup>327</sup> Mouse asthma in most models is a disease of the peripheral lung as opposed to the conducting airways. Additionally, genetic diversity issues are not addressed, because most studies are performed with Balb/C or C57B6 mice, which underpin multi-asthma phenotypes in humans. The popularity of the mouse as an experimental disease model organism is largely a result of the comprehensive analysis tools available for this species and the advent of gene targeting strategies, which permit manipulation of gene expression in a cell and tissue manner, and during different states of development. With the advent of clustered regularly interspaced short palindromic repeat (CRISPR) and CRISPR-associated protein-9 technology, genome engineering has progressed to the point that it is possible to edit genes to reflect even subtle mutations and investigation into the functional effects of single nucleotide polymorphisms identified in patient populations is possible. By contrast, genetic technologies have not been advanced in rat models (eg, Brown Norway Rats), which have previously been used to model allergic inflammation *in vivo*. Primate models (eg, *Ascaris* sensitivity in *Cynomolgus* or rhesus monkeys) are prohibitively resource intensive and ethically unacceptable in some countries; but should these models be used as an intermediate step between studies in rodents and human beings? Sheep and horse models of asthma have also been described, but their widespread use is limited by poor availability of resources and reagents for analysis. Excellent data exist on comparative mouse lung functional physiology but it is not widely understood, thus impeding progress on understanding the functional basis of episodic airflow restriction.

Few models exist that adequately address the interaction between viral (and bacterial and fungal) infections in asthma pathogenesis. This interaction

incorporates exacerbation models, and in particular the clinical reality, which is concomitant challenge with virus or allergen. Generally, models that attempt to address the issue of exacerbation focus on viruses.<sup>328</sup> A respiratory infection model for mice, including human rhinovirus, is under development and is the most applicable to humans, but is not really a good fit for human beings.<sup>329</sup> Most importantly, no models of the human rhinovirus-C subtype are available, which is the main pathogen in human beings associated with asthma. Additionally, evidence suggests that particularly during the initiation phase of asthma pathogenesis, bacterial pathogens play a central role as independent risk factors,<sup>330</sup> and likely also via interaction with viral pathogens, but few relevant experimental models are available to probe underlying mechanisms.

Generally, the scientific community still focuses exclusively on specific pathogen-free mice, which does not consider the microbiome perspective. This approach does not reflect the situation in human beings, in which the full spectrum of hygiene hypothesis-associated factors are relevant. For example, regulatory T-cell function is known to be completely different between specific pathogen-free and microbiologically conventional mice.<sup>331</sup> Moreover, microbial status during infancy determines maturation kinetics of both innate and adaptive immune functions and influences subsequent development of allergic responses.<sup>332</sup> A large-scale emphasis on immunologically competent adult animals exists, although the main caseload in human beings is in early paediatrics, which represents a vital difference considering that the immune system matures postnatally. Human epidemiology has shown that fundamental changes occur in lung and airway growth prenatally and postnatally as a result of immunoinflammatory episodes in the respiratory tract during pregnancy and infancy. This change helps to set a trajectory of lung and airway growth and differentiation, which influences development of lung function, but few studies have addressed this issue.

Translational biology (ie, mouse and human omics, genome-wide association studies, expression profiling) has not been systematically exploited. Technology to humanise mouse models is seldom used. The mouse is extremely well understood for drug kinetic analysis but this knowledge is rarely applied to allow inferential allometric scaling for mouse–human comparisons in academic studies.

Animal models should be designed around specific issues that emerge from the human studies on asthma cause and pathogenesis. For example, why do only around 25% of sensitised or exposed children have clinically significant airways symptoms, whereas 100% of sensitised or challenged mice respond? Why is it that more than 90% of hospital admissions among children aged between 5 and 16 years for severe asthma exacerbations occur during an acute virus infection, and

of these children, more than 80% (probably more) are sensitised to indoor allergens? Why are most asthmatic boys younger than 10 years, yet most of the ongoing animal work is performed using female mice?

The establishment of an integrated platform is needed, whereby animal models form part of a framework that includes in-vitro cell culture systems using cells isolated from patients. Cell culture analysis has progressed to the extent that it is possible to generate a lung-on-a-chip to investigate cultures containing multiple cell cultures, under dynamic flow, stretch, or inflammatory insult.<sup>333</sup> Respiratory medicine should not be afraid to use human in-vivo models to answer particular questions that might shed light on molecular mechanisms underlying disease pathways.<sup>334,335</sup>

## Overall conclusions and recommendations

The Commissioners collectively identified seven key recommendations, along with ideas for operationalising them and assessing their effect. We specify goals over the next 25 years.

### **1. Evolve from the use of umbrella terms to disease labels that allow for treatment guidelines to be more precise. What asthma do I have?**

The Commissioners considered what should become of the label asthma. Our recommendation is, as suggested before,<sup>336</sup> to use asthma solely as a descriptive label for a collection of symptoms (ie, more similar to arthritis than cystic fibrosis). Pathological breathlessness is necessary but not sufficient for the description; either or both of wheeze and abnormal cough are also needed. We make no assumptions about pathophysiology. The label asthma thus becomes the start, not the end, of the diagnostic and therapeutic process. The proper question to be addressed on an individual basis is, what asthma (or even airway disease) a patient has and how should it be treated? The logical consequence is that, as far as is possible, each patient's airway disease is deconstructed into component parts before planning treatment, focusing in particular on traits that are treatable and are reassessed periodically for further treatment adjustment.<sup>129</sup> This general approach is equally applicable in patients with COPD and removes entirely the need to consider overlap categories such as asthma COPD overlap syndrome.

Traits that are measurable, modifiable, and linked to morbidity have been identified. This is the start of the process and more well-defined traits might become apparent in time. We also advocate a new approach to the management and monitoring of patients with airway disease suitable for use in primary care in which the two dominant identifiable and treatable traits (risk of attacks associated with eosinophilic airway inflammation and symptoms as a result of airflow limitation) are assessed and managed, resulting in a more individualised and precise approach. This precision medicine approach is

supplemented by broad consideration of treatable traits that encompass overlapping disorders, comorbidities, and lifestyle and environmental factors. The simplicity of the approach, and the fact that it could be operationalised across different health-care systems, makes it an attractive alternative to current guidelines. It has the additional merit of identifying the important gaps that require further study.

We recommend that this approach becomes the basis for revised and combined guidelines for airway diseases in all but the most straightforward cases. Biomarker driven treatments and monitoring, including risk assessment, are important components, aligning the approach to assessments required in more severe disease in the new biological treatment era. We anticipate that this new approach will lead to more economical and effective use of treatment,<sup>10,175</sup> but this will need to be tested formally in appropriate health-care settings. Assessment and treatment costs and measures of treatment efficacy are therefore logical outcome measures to assess the efficacy of this new approach and, since the use of inhaled corticosteroids (particularly at high doses) will be affected most obviously by the management approach, we suggest that an achievable goal would be to reduce high-dose inhaled corticosteroid consumption by 30% with no overall loss of symptom control and better control of attacks.

## **2. Move beyond a disease control-based approach for asthma treatment**

We do not need more me-too steroids and long-acting  $\beta_2$  agonists. Resources should be directed toward asthma prevention and cure. Disease-modifying studies (eg, immunotherapy, early use of monoclonals) are required, which involves identifying biomarkers for risk in children, and a better understanding of initiation pathways for airway disease. We want to provide older patients with hope that their chronic asthma might be cured. Some encouraging initial progress has been made in this area.<sup>264</sup> Our goal is for at least one primary prevention strategy for high-risk children and one disease-modifying intervention for children and adults to be identified.

## **3. Emerge from age-associated and discipline-associated silos**

The clinical community needs to emerge from age-associated and discipline-associated silos and view airway disease in the context of the developmental trajectory from birth to old age. Regulators should be asked to enforce existing guidelines for mandatory testing plans for children as part of the licensing process for new asthma drugs. Exploration of the benefits of intervening in utero to prevent asthma is possible, as fish oil studies<sup>264</sup> and *Bordetella pertussis* vaccine studies have shown.<sup>337</sup>

Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network might still be difficult to

predict. For future research, the use of the correct principles and concepts is important. A reductionist approach is needed to identify involved mechanism and treatable traits, whereas systems biology needs to be implemented to address the complexity of the interaction between different components and ageing. Our goal is that the reductionist and system based approaches are used as complementary strategies, and that the right method is used for the right question.

## **4. Test before treatment**

Precision diagnosis and management cannot be implemented, nor can progress with prevention in children be made without moving away from the no-test culture that exists in clinical practice. Objective measures of key components of asthma are necessary, including measures of lung function in young children, measures of airway immune function, and measures of systemic and airway eosinophilia or neutrophilia.<sup>338</sup>

If about half of patients who eventually develop COPD in late adulthood already had abnormal lung function before the age of 40 years or even 6 years, early detection of this high-risk group is relevant. Reinforcement of smoking cessation advice in parents and adolescents,<sup>339</sup> the implementation of regular follow-up of lung function, and the initiation of treatment as early as possible is needed to avoid or delay disease progression. If lung development has been suboptimal, other organs might have also suffered similar developmental abnormalities.<sup>249</sup> Thus, the early identification of poor lung function by spirometry in early adulthood might have public health consequences that reach well beyond respiratory diseases. Spirometry is cheap and straightforward and several good opportunities probably exist to establish an early adult-life baseline, including in students entering university, young people applying for their driving licence, and young military personnel joining the army. Alignment of testing with a highly focused and effective educational campaign on the dangers of smoking might have a bigger effect than either in isolation. Properly designed, prospective studies are required to explore these hypotheses. The goal is to roll out a formal spirometry screening programme.

## **5. Zero tolerance for asthma attacks**

We advocate replacing the inadequate terms exacerbation or flare-up with attack and guideline groups, patient groups, and medical journals should be encouraged to implement this change. We hope that changing the name might change our weak responses to these sentinel events to something nearer that of cardiologists' focused, highly effective, and life changing response to a heart attack. The current one-size-fits-all approach to treatment and secondary prevention of attacks needs to be reviewed. Might a precision medicine approach offer more than the existing approach? Do biological drugs have a place

in the treatment of acute attacks of asthma? We will push research in these important areas across the spectrum of acute wheezing illnesses as the effect on health-care systems and patient outcomes could be considerable.

In terms of prevention, we anticipate that measuring biomarkers will help identify at-risk patients and perhaps help them decide to commit to life-long prophylactic treatment. We see value in the development of a risk score,<sup>272</sup> which could be incorporated into an annual review, and might help to move from secondary prevention to primary prevention of attacks. The Commissioners will drive the development and validation of this risk score. We have considered difficulties associated with severe (and sometimes fatal) attacks occurring in patients with previously mild episodic symptoms. To some extent these episodes are stereotypic and can be predicted by meteorological (summer thunderstorms, extreme cold) and social (return to school, increased indoor aeroallergen exposure, exposure to occupational sensitiser) events. We will lobby patient organisations, asking them to do more to identify and advertise high-risk periods and provide targeted and effective patient advice, perhaps with the support of media and social media. **The replacement of as-required short-acting  $\beta_2$  agonists with combination corticosteroid and fast-acting  $\beta_2$  agonist inhalers as reliever therapy in patients with episodic symptoms will need to be considered, depending on the results of ongoing randomised controlled trials. This regimen has the potential to have a considerable effect on the occurrence of severe unexpected attacks.<sup>29</sup>** Overall, we see this area as one in which considerable progress is possible and consider a realistic goal to be to reduce attack frequency, hospital admissions with acute attacks of asthma, and mortality by 50%.

## 6. Make the most of new treatment opportunities in severe disease

We have a big opportunity to improve outcomes in severe asthma. The treatable traits approach is particularly applicable and is likely to have a large effect as heterogeneity of clinical and biological aspects is more obvious in severe airways disease.<sup>25</sup> The biological era of treatments will begin around the same time as the publication of this Commission. We must be sure that we use these drugs effectively in individual carefully characterised patients. Basic aspects of management must be mastered before new therapies are introduced. Treatment adherence is a particularly important aspect and we will push for the further development of tests capable of identifying poor adherence and treatment approaches capable of improving it.

We are fortunate that simple and reliable biomarkers of response to biological treatments are available for children aged between 5 and 16 years and adults and potentially in those aged younger than 5 years.<sup>338</sup> We will need to move from a traditional disease category

symptom, and lung function-based assessment of treatment need and response to one in which decisions are driven by the presence and responsiveness of the relevant trait. We must make progress in establishing which biological drug is appropriate for which patient by collating data from phase 2 and 3 clinical trials and carefully collecting post-registration patient data with the goal of identifying responsive subgroups. Trial data must be made available for individual patient data analysis. This is another area in which considerable progress is possible. A realistic and an important goal from the patients' perspective is to reduce exposure to regular and rescue oral corticosteroids by 50%.

## 7. Better research

The Commissioners will work in collaboration with the pharmaceutical industry to ensure that future clinical trials establish not only treatment efficacy and safety but identify definable subgroups who derive particular benefit from treatment. The future will be delivering treatment to the right lungs rather than more treatments to more lungs. Trial populations should be selected on the basis of possession of the characteristic we are seeking to modify rather than arbitrary diagnostic labels, and we should align our primary and patient relevant outcome measures to those associated with the characteristic. Future trial populations should be sufficiently broad to ensure that potential covariates are fully evaluated rather than assumed to be important and excluded at the recruitment stage. This new approach will inform rather than obscure the identification of new treatable traits. We will end the irrational process of trialling bronchodilators in patients selected on the basis of the presence or absence of a bronchodilator response at baseline, and evaluating drugs that target eosinophilic airway inflammation in patients without this characteristic.

We suspect that these changes will be readily understood and accepted by regulatory authorities such as the Food and Drug Administration because their primary concern is that trials are done in well-defined populations. Currently this describes populations that have the diagnostic characteristics of the condition (ie, asthma or COPD) as set out by relevant guidelines. When the guidelines change, so will the authorities. However, we must ensure that the authorities are aligned to any proposed change. Our goal is for clinical trials of the future to focus on rational and well defined traits rather than arbitrary disease labels.

In epidemiology, we must stop assuming that asthmas across the globe are the same disease, and, just as we insist on testing patients before they are treated, we insist on testing before research—ie, which airway disease is actually being studied? Our goal is to move away from observational studies towards intervention studies, defining the components we are interested in and measuring them with much more precision, adopting novel adaptive research designs when necessary.<sup>340</sup> Animal models need to be more applicable to human

beings, including pregnancy exposures, and viruses and allergens, rather than just single factors. Despite the cost of large animal models, these studies represent an important stage between mice and human beings. Using a range of animal models will offer the best prospect for investigation of the complex interplay between different inflammatory pathways, establishing why aberrant inflammatory pathways perpetuate, and identifying preventive strategies.

Although considerable progress in technology and molecular biology has been made since the earliest use of cellular markers to guide treatment,<sup>2</sup> in airway disease very little has changed at all. How will the management and treatment of airway diseases have progressed in 25 years? The Commissioners hope that that objective, biomarker driven analysis of airway diseases will occur across the age spectrum, rather than the use of simplistic umbrella terms; that treatments will be pathway specific, and monitored by objective biomarkers of risk and impending loss of control; that adherence and need for treatment change will be promoted using real-time data transmitted to patients and physicians, with consultations using modern communication methods; and individuals at high risk in future generations (defined by molecular and omics biomarkers) will be targeted by preventive strategies to preserve lung function and lifelong lung health, which will be the main focus of therapeutic research. We want this approach to be incorporated into research, whereby the geographical diversity of airway diseases is appreciated not ignored; the sophistication of scientific studies will be matched by appropriate clinical assessment of the disease; and animal models will truly reflect human disease. This Commission represents an opportunity to initiate a decade or more of accelerated progress, delivering better outcomes and new treatment approaches for our patients.

#### Contributors

IDP and AB coordinated data collection and organised the Commission meetings and teleconferences. The Commission was drafted by IDP, RB, and AB. All Commissioners contributed to the concept, recommendations, writing, and editing of the Commission under the direction of the co-chairs.

#### Declaration of interests

IDP received grants from GlaxoSmithKline, Afferent and Atopix; and received honoraria and speaker fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GlaxoSmithKline, Dey Pharma, Merck Sharp & Dohme, Schering-Plough, Novartis, Napp Pharmaceuticals, Regeneron, Teva, Knopp, Chiesi, and RespiVert. RB received personal fees from the Health Research Council of New Zealand, GlaxoSmithKline, AstraZeneca, and Novartis; and received grants from AstraZeneca, Chiesi, Cephalon, Genentech, GlaxoSmithKline, Novartis, and Sanofi-Aventis. AA received grants and personal fees from AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, Menarini, and Novartis; and received personal fees from Teva and Chiesi. GPA serves on advisory boards for Novartis, GlaxoSmithKline, AstraZeneca, Pieris Pharmaceuticals, and Boehringer Ingelheim; and was employed on a sabbatical basis by AstraZeneca between 2015 and 2016. EB received personal fees from Sanofi, Novartis, AstraZeneca, Teva, GlaxoSmithKline, Vectura, and Boehringer Ingelheim; and received grants from GlaxoSmithKline, AstraZeneca,

Roche, and Novartis. GB received lecture fees and fees for advisory board membership from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva, and Zambon. AC received personal fees from Novartis, Sanofi-Regeneron, ALK, Bayer, Thermo Fisher Scientific, GlaxoSmithKline, and Boehringer Ingelheim. FMD received unrestricted donations from Boehringer Ingelheim, Merck Canada, GlaxoSmithKline, and Novartis; received a grant from Merck; and serves on an advisory board for Boehringer Ingelheim, outside the submitted work. JVF received grants from the National Institutes of Health, Pfizer, Genentech, and Vitareris; received personal fees from Boehringer Ingelheim, Dynavax, MedImmune, Theravance, and Peiris; his institution received a grant from the National Heart, Lung, Blood Institute; and is a named inventor on a patent describing biomarkers of Th2 high asthma and on a patent describing thiol modified carbohydrate compounds as novel mucolytic drugs, which provides no income. PG received grants from National Health and Medical Research Council Australia; and received personal fees from AstraZeneca, GlaxoSmithKline, and Novartis. LGH received grants from MedImmune, Novartis UK, F Hoffmann-La Roche, AstraZeneca, and GlaxoSmithKline; has sat on advisory boards and lectured at meetings supported by GlaxoSmithKline, RespiVert, Merck Sharp & Dohme, Nycomed, Boehringer Ingelheim, Vectura, Novartis, and AstraZeneca; has received funding support to attend international respiratory meetings from AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, and GlaxoSmithKline; received institution fees for participation in asthma clinical trials for GlaxoSmithKline, Schering Plough, Synairgen, and F Hoffmann-La Roche; and is the academic lead for the Stratified Medicine UK Consortium in Severe Asthma, funded by the Medical Research Council, which involves industrial partnerships with Amgen, F Hoffmann-La Roche, AstraZeneca, MedImmune, Aerocrine, and Vitalograph. MH received personal fees from Astrazeneca, Novartis, Roche, Sanofi-Regeneron, and Teva; and received grants and personal fees from GlaxoSmithKline. GM received grants from AstraZeneca and GlaxoSmithKline, and received speaker fees from Novartis Pharmaceutical and the International Union Against Tuberculosis and Lung Disease. FDM received grants from the National Institutes of Health, the National Heart, Lung, Blood Institute, the National Institute of Environmental Health Sciences, the National Institute of Allergy and Infectious Diseases, the National Institutes of Health Office of the Director, and Johnson and Johnson; and received personal fees from Copeval and Commense. EvM received personal fees from PharmaVentures, OM Pharma, Decision Resources, Novartis Pharma SAS, The Chinese University of Hong Kong, the University of Copenhagen, HAL Allergie, Ökosoziales Forum Oberösterreich, Mundipharma, the American Thoracic Society, AbbVie, the University of Tampere, the European Commission, Massachusetts Medical Society, and the American Academy of Allergy, Asthma and Immunology. SW received grants and personal fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Genentech, Sanofi-Regeneron, and Novartis; and received personal fees from Knopp. PC, UF, PGH, CML, PDS, HJZ, and AB declare no competing interests.

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