Elsevier Editorial System(tm) for The Lancet
Manuscript Draft

Manuscript Number: THELANCET-D-16-01609R2

Title: After asthma - redefining airways diseases. A Lancet commission

Article Type: Other

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Abstract: No abstract for this article type

After asthma – redefining airways diseases. A *Lancet* commission

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'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' Kola and Bell[1]

Executive summary

Asthma is responsible for significant global morbidity and health care costs. Significant progress was made against key outcomes such as hospitalisation and asthma mortality in the 1990's and early 2000's but there has been little improvement over the last 10 years despite escalating treatment costs. New assessment techniques are not being adopted and progress in new drug discovery has been slower than in other specialities.

In this document we set out to provide our view of where we are and where we need to go as a community of clinicians and researchers who tackle the significant public health problem that is asthma. The document should be seen not as a comprehensive review but more of an opinion article, reflecting the collective view of the Commissioners (referred to hereafter as we). It is also a call for action to all clinicians involved in the field. The aim of the Commission was to identify entrenched positions where progress has stalled and to challenge dogma, and the results have been integrated into seven sections.

In the first section of the document we argue that our physiology-based classification system for airway disease is outdated as it provides a very limited perspective on the heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in our patients. The quote at the start of this section, from a recent review discussing poor progress in new drug discovery, is particularly pertinent. It is now clear that our over simplistic concept of disease, and assumption that all asthmas are the same, nearly resulted in us missing the significant clinical benefits of Corticosteroids[2] and Mepolizumab, a monoclonal antibody targeting the type 2 cytokine interleukin (IL)-5[3]. These entrenched concepts are, we believe, the most important causes of a stalling in improvements in key clinical outcomes in the last 10 years despite ever increasing spending on asthma treatment[4].

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 we use and acknowledge the assumptions that go with them. Airway diseases should be deconstructed into traits that can be measured and, in some cases, modified (treatable traits), and which are set in the context of

social/environmental factors and extra-pulmonary co-morbidities. An important catalyst for this change has been the discovery of simple and clinically accessible measures of one of the most influential and treatable trait: eosinophilic airway inflammation[5]. 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[6] and the use of these biomarkers to stratify patients has been instrumental in recent successful new drug development[7,8].

The second section considers how this new approach could be operationalised in all healthcare 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 (ICS) are used in a more targeted, biomarker directed and hopefully efficient way. The Commissioners considered at length the risk that moving from a 'more ICS in more lungs' to a 'more ICS in the right lungs' approach might jeopardise the large improvements in key outcomes seen between 1990 and 2005 with the former approach. An important missing bit of information is the long-term safety of withholding ICS in patients with low biomarkers of eosinophilic (or type-2) inflammation. Our pragmatic solution is to use an as required combination low-dose ICS/rapid onset β_2-agonist inhaler as the default reliever option so that patients with episodic symptoms and airway inflammation are more likely to receive ICS at a critical time, while acknowledging that this approach needs to be tested. We suggest that ICS treatment is not escalated beyond this unless biomarkers of type-2 inflammation are increased. There is a substantial rationale for this approach and support from clinical trials[9]. Once established on treatment we need to improve monitoring from 'how are you?' 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 for our views on the development and evolution of airway diseases through infancy, childhood and adult life. Much more needs to be done to allow this proposed deconstruction of airway disease in non-invasive ways across the age spectrum. Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network may still be difficult to predict, in part because these mechanisms are superimposed on a system that is developing in childhood and declining during senescence. In order to make sense of this additional complexity it is important that the correct principles and concepts are used. Dominantly, a reductionist approach is used to identify involved mechanism and treatable components, which can lead to novel drug developments or therapeutic

concepts. On the other hand, if we want 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 in order 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, but also that we need to move on from current birth cohorts, informative though these have been, if we are to address the fundamental causes of asthma, and move beyond satisfaction with the status quo and toward an ambition to prevent or cure asthma.

When thinking about asthma treatment we tend to focus on established asthma, rather than the fundamental underlying causes. This has set the agenda for asthma as a chronic disease that we should try to control rather than one we should try to conquer. The fourth section asks whether we can modify the inexorable progression from intermittent early childhood wheeze to persistent asthma in the teen years followed by a life sentence of therapeutic drug dependence. We call for no more 'me too medicines' but a commitment to develop treatment approaches that focus on prevention and cure.

The next two sections discuss two areas where 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[10,11] or with highly selective biologics inhibiting type-2 inflammation[12]. The use of as-required ICS/rapid onset β_2-agonists 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 figure 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[6,7,13]; however, we must use the tools of modern molecular and systems biology to tease out even better biomarkers of risk and treatment response. Their use will be essential for us to make the most of the increasing numbers of new treatments that selectively inhibit type-2 inflammation.

We finish with a section calling 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 lacking any precision, such as 'Dr-diagnosed asthma'), and we should choose an outcome measure related to this trait and relevant to patients. Using models because they are there (systemic sensitization of mature mice, for example) 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 FDA, reviewers of manuscripts and grant funding agencies are rightly concerned that trials are carried out in well-defined populations but must this mean that they have the diagnostic characteristics of an arbitrary condition (i.e. asthma or COPD) set out by current guidelines? We think not, but we must ensure that all of these stakeholders are aligned to any proposed change.

Perhaps ambitiously, we propose a revolution in thinking about asthma, generalizable to all airway diseases, which, alongside the undoubted importance of optimal delivery of the best care to each patient, will deliver real precision asthma medicines, dissecting airways disease into its components 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 shake us out of a rut, diverting us away from a diagnostic and therapeutic *cul de sac* and result in a new system that will be valuable in epidemiological and interventional studies and make it more likely that we unpick pathophysiology and, eventually, develop better medicines and achieve better outcomes for our patients. We hope it will add momentum to the recent encouraging progress in new drug discovery and, as did the first asthma guidelines 27 years ago, lead to a decade or more of improved outcomes. We finish by formulating seven key recommendations and summarising our views on how these could be developed to the benefit of our patients (box 1).

"Wherefore is this* disease different *from* all other diseases*?" Maurice Pappworth

INTRODUCTION

It is 27 years since the first asthma guidelines were written[14-17], and "asthma" was identified as a disease associated with airway inflammation. This led to the much more widespread use of inhaled corticosteroids (ICS) instead of repeated and even regular doses of short acting β_2-agonists (SABA) as primary treatment, with great benefit to many patients (figure 1). However, progress has slowed over the last 10 years despite increased spending on treatments[18] and we have not seen the developments in new drug discovery enjoyed by other specialties[19]. Our central position is that the most important cause of this stagnation is a continued reliance on outdated and unhelpful disease labels, treatment and research paradigms and monitoring strategies, which have reached the stage of unchallenged veneration and have stifled clear thinking.

Imagine a rheumatologist diagnosing 'arthritis' or a haematologist 'anaemia' and generically treating without determining the specific type and cause in the 21st century. The notion is ludicrous. Yet, the umbrella term 'asthma' continues to be applied to the disparate group of conditions characterised by varying degrees of airflow obstruction (both fixed and labile); different (or no) patterns of inflammation; contributions from bacterial and viral infections which vary over time; an over sensitive cough reflex; and mucus hypersecretion. Despite a proliferation of research papers studying the pathology of asthma and identifying fundamentally different patterns of disease, especially airway inflammation, we are still stuck with this stereotypic label, and asthma therapy has really not progressed much over the last 20 years; it is still 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[20]. This simplistic chain of reasoning has become that wheeze or cough equals asthma equals eosinophilic airway inflammation equals need for prescription of ICS. If by chance the symptoms have the temerity to persist, this means that eosinophilic inflammation is refractory and more treatment must be given.

Concern about outdated disease taxonomy was expressed by our forefathers in 1958[21] and again in a Lancet comment in 2006[22], but little has changed. A catalyst for change has been the development and clinical use of non-invasive methods to assess airway inflammation[5]. These techniques have shown that 'asthma' and other airway diseases consist of a heterogeneous mix of pathologically distinct processes poorly represented by our current physiological and symptom-based classification system[6,7,23] and have opened the door to a new precision medicine type approach to management. Eosinophilic airway inflammation has emerged as particularly important as it is readily recognisable

and is associated with the risk of attacks that can be prevented with corticosteroid treatment[6]. 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[10,11,24,25], and the same basic approach works well irrespective of the diagnostic label. Moreover, it has been shown convincingly that biological agents that specifically inhibit eosinophilic airway inflammation by blocking the type-2 cytokines interleukin (IL)-5, IL-13 and IL-4 have important beneficial effects when given to adult patients with airways disease and this pathology, but not when evaluated in all comers with 'asthma'[3,12,26-29]. It is now clear that a new form of stratification of airway disease will be essential if we are to make the most of the opportunities provided by these new biological treatments. The *absence* of eosinophilic airway inflammation is also important – it means that ICS should not be escalated, with all the attendant risks of side-effects, and new treatment possibilities should be considered.

Our concern is that continued reliance on an approach that over-simplifies and over-generalises a complex and heterogeneous syndrome ('asthma') will result in us missing other pathogenically important and tractable mechanisms. New thinking is needed and we hope that this Lancet Commission will stimulate this. The Commission is predicated on the assumption that 'asthma' is no more a 21st century diagnosis than 'arthritis'[30], and will attempt to liberate this mix of airway diseases from the protective but limiting diagnostic label 'asthma' to reflect the clinical and pathologic heterogeneity of different "asthmas" and allow the management of these diseases to progress to the next level.

The commission asked experts in a large number of fields, linked by a common expertise in asthma, to consider where thinking and management should be in the 21st century, and how best to get there. An important early goal was to move out of age (paediatric, adult), discipline (basic science, epidemiology, and clinical research), disease and nationality related silos and attempt to think in a joined up way. Our list of Commissioners, all acknowledged experts in their respective fields, were chosen to reflects this goal. The Commissioners met in person on three occasions between November 2014 and September 2016 and participated in numerous teleconferences. Each Commissioner identified ten areas where they felt progress was most pressing. These 'points for progress' were organised into seven themes and working groups were assembled to discuss each (box 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 positions where progress has stalled and to challenge dogma. Each theme addressed the same questions:

1. Where are we now?
2. Where do we think we want to go?

This Commission would be a sterile process if we did not set ourselves goals and we finish by identifying seven key recommendations (box 1), along with our ideas for operationalising them and assessing their impact.

SECTION 1: CHANGING THE WAY WE THINK ABOUT AIRWAYS DISEASE

Developments in thinking on 'Asthma' over the years

Asthma has been recognised since antiquity. The word comes from the Greek ασθμα, meaning a 'short-drawn breath, hard breathing, or death rattle' (box 3) 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; there was also recognition of an association with environmental factors, including climate and geographical areas. Sir John Floyer[31], who suffered from asthma, provided the first modern treatise on the disease in 1698 (box 3), and identified bronchial constriction as a cause for wheezing. He was also the first to describe asthma attacks and potential triggers by providing a first-hand account of his own experiences. Salter[32], himself also an asthmatic, provided a more formal definition of asthma in the late 19th century (box 3) and recognised that asthma *' …. if it is at all severe and its attacks frequent , cannot long exist without inflicting permanent injury to the lungs..'*. This 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 impact of this condition (box 4).

Francis Rackemann, a distinguished Boston physician, carried out 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[33]. 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.'* 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 intrinsic to the body associated with older age at onset and the absence of atopy[33].

The association of asthma with variable airflow obstruction was formally recognised soon after spirometry was introduced by Hutchinson in the 1840s and the association with a low forced expiratory volume in one second/vital capacity (FEV_1/VC) ratio was described by Tiffeneau in the 1940's[34]. Bronchodilator reversibility has emerged as the diagnostic test of choice although the validity of this test has never been properly addressed[35] nor has it been recognised that this test tells us nothing about the presence and nature of underlying airway inflammation. Bronchodilator treatments, including epinephrine, anticholinergics, methylxanthines, and inhaled β-agonists were all introduced in the first half of the twentieth century and, early in the second half, systemic corticosteroids were identified as a potentially useful treatment. The introduction of systemic corticosteroid treatment in the 1950's in the UK was not entirely straightforward as an early and influential MRC sponsored clinical trial showed little useful efficacy and highlighted a high potential for systemic toxicity[36]. Harry Morrow-Brown, a young chest physician working in Derby, England was surprised by these negative findings and went on to use his medical student microscope to show that there was clear efficacy in patients with asthma who had eosinophils present in their sputum smear but not in those without[2]. He used a similar method of patient selection to show in the early 1970's that inhaled Beclomethasone Dipropionate was an effective topical treatment when administered by aerosol and that treatment mitigated the adverse effects of oral corticosteroids by allowing a significant number of patients to withdraw this treatment without loss of asthma control[37,38]. This work was widely ignored over the next 50 years but in retrospect was pioneering and important as 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 been long appreciated in paediatrics, and a large number of studies can only briefly be summarised here. In the 1960's, both Selander[39] and Fry[40] in different contexts astutely observed that episodes of infant wheeze were temporally associated with outbreaks of viral infection in the community, but these infant wheezers did not develop asthma in childhood. Jeremy Cogswell, a general paediatrician in Poole, took the matter further in a small but stellar study showing that early exposure to house dust mite was of great importance to the development of early childhood asthma, but was irrelevant to wheeze in infancy[41,42]. More long-

term studies have confirmed that there are a number of different patterns of wheeze. The Melbourne cohort, which has reached the sixth decade with around 75% retention, has shown that lung function tracked throughout the study period, with those who just wheezed with viral colds ('wheezy bronchitis' as it was initially described) having normal lung function throughout the life course, but children with asthma, and particularly severe asthma, having permanent obstructive defects. Indeed, the children with severe asthma had a more than 30-fold increased risk of 'chronic obstructive pulmonary disease (COPD)', and this group had the worst lung function at age 10 years[43]. The clinical differences between those who wheeze with viral colds and 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[44].

Perhaps the classical cohort study was from Tucson, which followed babies from birth and initially reported on wheeze at two time points, age three and six years[45]. The timing of study visits meant that only four wheeze phenotypes could be discerned: never wheeze, transient early (0-3 years only), persistent (0-6 years) and late onset (3-6 years), with different characteristics and evolution over time of lung function. Mathematical modelling in big cohorts with more data points or information from healthcare records (ALSPAC, PIAMA, KOALA, Dunedin, Manchester, Rotterdam)[46-52] have discerned more phenotypes concluding that subtypes of childhood wheezing can be identified based on the temporal pattern on wheezing. However, there were important differences 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[53]. These studies have identified numerous potential risk factors for asthma onset, including maternal asthma[54] and smoking in pregnancy[55]; mode of delivery[56]; low birth weight[57]; impaired lung function[58,59] and airway hyperresponsiveness shortly after birth[60-62]; and the importance of early microbiological exposures[63]. Also, just as it has long been appreciated that all wheeze is not equal, it is becoming clear that there are different patterns of atopy, with differing significance[50,64-67]. Hence the combination of sensitisation to multiple allergens and persistent wheeze with acute attacks is most predictive of a long term adverse outcome[51,66,67]. Finally, the differences between the factors *initiating* atopic asthma, and those propagating the asthmatic condition, have become appreciated. Three excellent randomised controlled trials of the early initiation of ICS in infants at risk for the development of asthma have relieved symptoms but shown no effect of this treatment on the natural history and progression of wheezing[68-70], and the limited studies of the pathology of infant wheeze have shown no eosinophilic inflammation in most[71], whereas of course properly

administered ICS are excellent suppressive treatment for recurrent or persistent asthma with eosinophilic airway inflammation.

Over the last 50 years it is possible to identify two main eras of asthma management each lasting about 25 years: the bronchodilator era, starting with the introduction of increasingly selective inhaled β_2-agonists in the mid-1960's and focusing on airway hyperresponsiveness as the key pathophysiological abnormality; and the anti-inflammatory era, starting in the late 1980's, where more aggressive use of ICS was emphasised and airway inflammation was seen to be of central importance (figure 1). It should be noted that, despite clear evidence of lack of correlation between inflammation and airway responsiveness, and the differential response of each to different treatments[72] the myth that airway inflammation was the origin of all asthma troubles was sedulously cultivated. This 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 hospitalisation rates with 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 β-agonist or high dose poorly selective β_2-agonist inhalers[73-75] (figure 1). Underuse of ICS has also contributed to asthma deaths (and depressingly still does)[76]. This association, and the increasing recognition that airway inflammation was commonly seen even in patients with mild asthma[77], fuelled the second era. However, over-reliance on inhaled β_2-agonists still contributes to asthma deaths[78].

Increased use of ICS proved to be a more difficult sell than the use of β_2-agonists, in part because treatment had a less rapid and therefore less obvious impact on symptoms. Guidelines were used to encourage patients and prescribers to introduce ICS earlier and patient education with multidisciplinary input was employed to encourage continued adherence with treatment once a symptom response had occurred. This second era was associated with an impressive reduction in hospitalisation rates and mortality from acute asthma, particularly over the ensuing 10-15 years in children (figure 1). Corticosteroids do not totally obliterate acute bronchodilator reversibility; one third of patients in the Brompton severe asthma registry still have reversible airflow obstruction despite a depot injection of triamcinolone[79]. It became clear that combinations of inhaled long-acting β_2-agonists (LABA) and ICS resulted in superior outcomes for many[80,81]. However, worryingly, at least in children and despite the complete absence of any evidence, there is an increasing trend to prescribe combination therapy as first line preventers. Still more worryingly, it is possible to

prescribe LABA as a single agent, despite compelling evidence that: (a) people use them without concomitant ICS; and (b) this increases the risk of asthma deaths[82].

It is of great concern that progress against key outcomes has stalled in the last 10 years and preventable deaths continue to occur with depressing regularity despite increased investment in treatment. This could be explained partly by variations in practice, as there are marked regional and international differences in these outcomes, related in part to access and affordability of asthma therapy as well as variations in asthma symptom prevalence[83,84] (figure 1 and 2). In Finland, for example, a well-coordinated and highly effective national campaign focusing on asthma control resulted in a marked reduction in hospitalisations due to asthma[85]. However, although the overall approach was found to be cost-effective, treatment related costs were significant, and the guideline and self-management approach that were the cornerstone of the Finnish approach have been more difficult to implement elsewhere. There is also a more fundamental concern that our current 'one size fits all' management approach cannot be safe and deliver better outcomes to everyone even despite greatly increasing treatment costs, unless our diagnostic and management paradigms are optimised.

Where are we now?

Definition and basic concepts

The most widely used Global Initiative for Asthma (GINA) 2002 definition of the disease (box 2) is a lengthy description of pathological, physiological and clinical features that encompass the major disease characteristics (airway hyperresponsiveness, structural changes to the airways or airway remodelling, disordered mucosal immunity and chronic airway inflammation)[86]. The latest 2014 definition (box 2)[87] is less descriptive and moves away from these features but, nevertheless, they are still commonly highlighted as important.

Implicit in making abnormalities in airway physiology, airway structure, and airway immune function part of the definition of 'asthma' is that these abnormalities are well defined, homogeneous, universally present, causally linked and readily measureable. The reality is that they are none of these. Although we can measure abnormalities in airway physiology, we cannot easily measure abnormalities in airway structure, or airway immune function. This is a problem as promising treatment approaches for the abnormal airway response to viral infection[88] may not succeed until we have new techniques to assess this component. Similarly, improving airflow limitation is an important goal of management, but we will not be able to modify this until we can distinguish

between the limitation that is due to an active, treatable factor and that which is irreversibly programmed in early life or prenatally.

Diagnostic and monitoring approach

Despite the protean manifestations of 'asthma' discussed above, our main approach to diagnosis has been to document asthma symptoms and variable airflow limitation, and this approach has changed little in 50 years. Reliance on measures of airflow obstruction is problematic for six reasons.

(i) Lack of consensus on how to demonstrate variable airflow limitation. Definitions of abnormality are not closely related to the normal range for that measure (i.e. bronchodilator reversibility). Moreover, the measurement characteristics of different tests are not well studied[89] 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 where the clinical question is whether a symptomatic patient has 'asthma' or an alternative explanation for their symptoms. Some tests (i.e. peak expiratory flow variability) have been shown to be grossly abnormal in patients with very pathogenically different conditions such as dysfunctional breathing or vocal cord dysfunction[89]. There is thus a large potential for misclassification.

(ii) Difficulty measuring lung function in primary care. Tests of variable airflow limitation are relatively difficult to do in non-specialist settings where most cases of asthma are diagnosed, but also in pre-school children in any clinical context. This is particularly the case for assessment of airway responsiveness. This is unfortunate as tests of airway responsiveness are sufficiently sensitive that a negative result provides strong evidence against a diagnosis of asthma. A result of the relative difficulty of pulmonary function tests in in the primary care setting and the absence of rule out tests has been that primary care clinicians feel they have few options other than a 'trial of treatment' approach with ICS. This approach is flawed because the mimics of asthma (which often do not respond to corticosteroids) cause variable symptoms and may therefore improve spontaneously over time, leading to the mistaken belief that ICS treatment 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 (i.e. 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, together with the tendency of clinicians to be cautious in borderline cases, increase the likelihood that patients may be

started on inappropriate ICS therapy, with associated cost and potential toxicity. There is increasing evidence that over treatment is common: observational studies showing that 60% of patients referred to secondary care[90] and 30% of patients in primary care[91] have no objective evidence of airway dysfunction or inflammation and do not deteriorate when ICS treatment is stepped down. One result of inhalers being given away free with Cornflakes is that the diagnosis of asthma has become trivialised. This may be one of the reasons we struggle to sell the need for long-term treatment to an increasingly sceptical population.

(iii) Identifying at risk patients. Current diagnostic approaches for asthma do a poor job identifying patients who are at high risk for serious outcomes. This problem is evidenced by data from national enquiries into asthma deaths showing that patients with asthma perceived to be mild and low risk continue to die of the disease[78]. Strategies are needed that identify high risk disease more clearly, and engage patients in ways that encourages 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.

(iv) Disadvantages of umbrella diagnostic terms. Conventional wisdom is that asthma and COPD are distinct, and guidelines suggest very different management approaches[86,87,92], particularly in the way we use ICS. The reality is that there is very significant overlap, 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[93]. The clinical communities response to this overlap has been to invent another umbrella term: Asthma COPD Overlap Syndrome (ACOS)[94]. This acronym has the demerits of combining what we argue to be two problematic umbrella terms to make a third one that is even more problematic[95]. ACOS may be characterised by a COPD-like systemic inflammatory profile; ACOS, asthma and COPD may be neutrophilic, eosinophilic or mixed; and bronchodilator reversibility fails to distinguish anything from anything else[96]. 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 irrespective of the label[96,97]. Given that this is the case for many features of 'asthma' and 'COPD' then the importance of applying the label becomes questionable and it may even be counterproductive because of the clear potential for misclassification and inappropriate use of ICS and LABA monotherapy.

(v). Poor treatments for poorly characterized airway diseases. Failure to look beyond our current diagnostic labels limits exploration of causes of morbidity in patients who have chronic cough or wheezing associated with viral respiratory tract infections. These are airway diseases with a relatively distinct clinical phenotype but they are not easily placed in the current classification system for asthma or COPD. As a result, we have only a superficial understanding of the mechanisms of these common problems and no specific treatment approaches. Many patients sit uneasily under the 'asthma' umbrella and receive regular asthma treatment with little evidence of benefit. Our failure to clearly identify and study these specific patient populations means that there is almost no interest from industry, and thus few prospects for effective treatments.

(vi) *Equation of variable airflow obstruction with eosinophilic airway inflammation*. The identification of variable airflow obstruction in the definition and diagnostic process for asthma may be one reason why it is widely assumed that this pattern of airway dysfunction identifies a discrete airway pathology (eosinophilic airway inflammation). This is now known to be incorrect[26]. Severe eosinophilic airway inflammation may even be associated with loss of bronchodilator reversibility[98] and 40-50% of patients with objective evidence of variable airflow obstruction have non-eosinophilic pathology (or no detectable airway inflammation)[99]. Thus, whilst 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 disconnect between defining characteristics of 'asthma' and outcomes that really matter (risk of attacks, likelihood of a response to corticosteroid treatment) may be another reason why clinicians have tended to adopt a 'no-test' approach to diagnosis. However, we have seen rapid progress in the development of biomarkers of airway inflammation. For instance, we now have several reliable markers of eosinophilic airway inflammation, which provide a better perspective on risk of attacks[100,101] and the likely response to treatment with corticosteroids[6,101,102] than traditional physiological measures (table 1). Some of these biomarkers (i.e. 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[6]. There is increasing evidence that these biomarkers stratify risk effectively and results in more effective and economical use of currently available and new treatments[6,25,101]. The howls of rage from some quarters at the suggestion by the UK National Institute for Clinical Excellence (NICE) 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 instituted, without any objective diagnostic measurements ever being made. Is there any other chronic disease for which objective diagnostic tests are readily available of which this can be said? Although the Commissioners differed in their views on the strength of evidence for diagnosis and management guided by biomarkers, particularly in children, there was a consensus that the incorporation of biomarkers into the diagnosis could only enhance the capacity to diagnose asthma responsive to ICS and lead to a paradigm shift from the current approach to diagnose the umbrella term asthma, to the diagnosis of asthma phenotypes that respond to specific treatments.

New drug development

Until recently we have not seen the developments in new drug discovery enjoyed by other specialty areas (table 2)[19]. This area perhaps exposes the limitations of our current view of 'asthma' and airway disease most obviously. New asthma treatments are largely variants on the old; a browner inhaler, with more potent topical effects, despite increasing concerns about topical immunosuppression[103]. When new treatments become available, they are widely prescribed to all comers despite being largely ineffective (Sodium Cromoglycate, Ketotifen) or effective only in subgroups of patients (Omalizumab, Mepolizumab). There has been, until recently, no concept of targeted treatment. 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)[19].

Mepolizumab, a humanised monoclonal antibody that was developed to inhibit eosinophilic airway inflammation by blocking interleukin (IL)-5, is a good example. Mepolizumab was found to be safe and effective at blocking IL-5 and reducing eosinophilic airway inflammation when tested with *in vitro* systems and *in vivo* models[104,105]. A subsequent clinical trial was designed based around incorporating Mepolizumab into a step-up guideline-based paradigm[106]. Within this paradigm, Mepolizumab was investigated in patients who remained symptomatic on current ICS therapy and the clinical trial focused on lung function and asthma symptoms as traditional outcome measures. Despite adequate power, this trial was unexpectedly negative. This led to much soul-searching and the near-abandonment of the drug[107].

Investigators who were experienced with non-invasive measures of airway inflammation identified two important problems with this initial clinical trial: first, the heterogeneity of airway inflammation in severe asthma meant that a significant number of the trial participants would not have had eosinophilic airway inflammation and therefore would not be expected to respond; and second, the

occurrence of asthma attacks is closely linked with eosinophilic airway inflammation[13,26,107,108] and might have been a better outcome measure than lung function and asthma symptoms. Two investigator-initiated studies were designed targeting Mepolizumab specifically to patients with severe asthma and sputum eosinophilia and using asthma attacks as an outcome[26,108]. In both studies, Mepolizumab treatment was associated with decreased asthma attacks with effect sizes of 50% - 80% (Figure 3)[109]. Subsequent phase 2b[12] and 3[110,111] studies 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 obstruction and symptoms, previously regarded as essential defining characteristics of asthma, were of no value in predicting treatment response[12,98], nor seemingly was the label of asthma as robust treatment responses were seen in patients with features of COPD provided there was evidence of eosinophilic airway inflammation[12]. The same general principle has been instrumental in the development of a range of biological agents targeting IL-5[112,113], IL-13[28,29] and IL-4 & 13[27] pathways, many of which are showing encouraging 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 takes into account the increasingly recognised heterogeneity of asthma and offers precision management based on a careful assessment of the characteristics of a patient's disease and targeted treatment. This will be particularly important if we are to take advantage of the bounty of drugs that inhibit type-2 inflammation. It is also necessary in order to identify other pathogenically important and tractable mechanisms.

One important question is whether the phenotypic heterogeneity of asthma can be explained by discrete mechanistic pathways, or endotypes[114]. For example, it is possible that the systemic inflammation associated with obesity and older age may have effects in the airways to worsen asthma[115]. This is a complex area as there is a limit to how much phenotypic heterogeneity can inform our understanding of endotypes because many phenotypic traits (i.e. symptoms, airflow obstruction) can be caused by multiple disease mechanisms[114,116], just as 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 may represent a better conceptual framework to accelerate progress towards personalized treatments[116-119]. We can focus short-term

on these treatable traits while searching for mechanistic underpinning. The important principle is that mechanisms ultimately will drive the precision.

Treatable traits

Any biological tube reacts with a very limited and stereotypic set of responses, *irrespective of the underlying cause*. This is hardly a revolutionary concept: irrespective of how it is damaged, the failing kidney cannot excrete creatinine, and blood levels rise. Based on the thinking of the late, great Freddie Hargreave[120], and with the introduction of several new traits, the stereotypic responses of the airway to adverse events are (in rough order of importance and recognisability) any or all of:

Airflow limitation

This is a treatable trait if due to repeated contraction of airway smooth muscle and perhaps airway wall inflammatory oedema (mural); and/or intraluminal factors (airway secretions). However, variable airflow limitation may be due to less treatable problems such as loss of alveolar guy ropes (extramural). All that wheezes is not airway smooth muscle contraction, and the cause of wheeze and its response to treatment needs to be appreciated. Furthermore, paediatrics challenges the conventional view of airway hyperresponsiveness; just as there are multiple atopies (discussed below), there are multiple hyperresponsivenesses. Three prospective birth cohort studies have demonstrated that airway hyperresponsiveness is present within weeks of birth, at a time when there is no evidence of allergy, airway inflammation or increased airway smooth muscle mast cell infiltration[121], and is strongly predictive of medium term respiratory outcomes[60-62]. Animal and a limited amount of human data suggest the underlying cause is change in airway dimensions (elongation and narrowing) and loss of airway tethering points, such that any narrowing of theairway leads to an exaggerated obstructive signal[122]. Multiple subsequent additional and potentially more treatable factors are likely to contribute including sensitisation of airway nerves, mast cells and smooth muscle by inflammatory mediators[123]; reduced epithelial barrier function; reduced production of bronchoprotective factors[124]; an intrinsic abnormality of airway smooth muscle[125]; and some of the structural changes to the airway discussed below[123].

Airflow limitation may be unresponsive to bronchodilators and anti-inflammatory treatment. While this may not be a treatable trait, fixed airflow limitation is certainly one that can lead to overtreatment if not appreciated. Early life factors may be the most important causes of the airway structural changes leading to fixed airflow limitation[47,126-128]. The birth cohort studies show that these first develop antenatally and in early childhood and studies in adults show that, although there

is a subset of patients with rapid deterioration in spirometry, many people, with or without asthma or COPD, have normal lung aging[129]. Early lung function loss may be related to circumferential narrowing or elongation of the airway itself, which may be developmentally determined in utero[130], or postnatally, related to viral infection (obliterative bronchiolitis)[131,132] and pollution[133]; or loss of the alveolar tethering points (an important mechanism maintaining airway calibre is the alveolar 'guy rope' attachments; there are animal data that these are reduced by antenatal smoke exposure[134]). Airflow limitation has been demonstrated soon after birth, for example in the infants of mothers who smoked in pregnancy[135], long before there is any evidence of airway inflammation[71,136]. It can be worsened by antenatal or postnatal exposure to pollution[133], again likely independent of eosinophilic airway inflammation. The consequences of pre-term birth and early life bronchopulmonary dysplasia are another increasingly recognised cause of fixed airflow obstruction in later life[137].

The presence of a significant number of patients with asthma who have fixed airflow limitation provides a clear potential for clinically important misclassification if umbrella terms continue to be utilised. This problem disappears if we move towards a more precise and clinically useful approach that uses only the term "chronic airway disease" (like anaemia, see above) and, then, goes on to describe the particular treatable traits present in a particular individual. Definition of fixed obstruction may not be easy in an individual, and in children in particular there is no agreed definition of an adequate treatment trial for this purpose. Sometimes airflow obstruction is apparently fixed but responds well to anti-inflammatory treatment, presumably as a result of improvement in airway oedema and/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 lacking.

New imaging techniques and more sensitive physiological measures might provide new and clinically important information about mechanisms leading to fixed and variable obstruction, but until then the underlying causes of airflow limitation cannot be assumed to be always due to discrete treatable traits. We suggest that 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 may be necessary to do this.

Airway inflammation

Airway inflammation is heterogeneous among patients with a label of 'asthma'. Eosinophilic airway inflammation is an important pattern as 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 the master regulator lymphocyte population and probably also in their responsiveness to treatment with ICS (see figure 4)[138], and there may be others, hitherto undiscovered. The exact mechanisms and the clinical implications of involvement of these different pathways remain to be defined but they could theoretically represent individual distinct treatable traits. Given the proliferation of high cost monoclonals, we need to understand pathways in the individual patient rather than go forward with a haphazard series on N-of-1 therapeutic trials.

Prospects for identifying and modifying airway inflammation in Type 2 low disease are much more uncertain[139,140]. We have therefore not included this as an individual treatable trait. Some encouragement that it might be is provided by the beneficial effects of long-term low dose macrolides in patients with non-eosinophilic asthma[141,142] but CXCR2 antagonists, which cause a marked reduction in sputum neutrophil counts[143], have no efficacy in patients with uncontrolled asthma[144]. In patients with COPD macrolides and CXCR2 antagonists have very different effects in smokers and ex-smokers, with the latter effectively reducing exacerbations in smokers but not ex-smokers[145] and the former having the opposite effect[146]. These findings suggest that there are at least two types of neutrophilic airway inflammation in patients with airway disease, differing in their relationship with smoking and airway infection. Indeed, neutrophilic inflammation may be *beneficial*[147] in the presence of airway bacterial infection (which is increasingly implicated in asthma, below), as a recent cystic fibrosis (CF) trial of an anti-LTB_4 strategy demonstrated[148]. The important lesson of this trial was the mere presence of inflammation is not a sufficient reason for obliterating it.

Neutrophilic airway inflammation might also be driven by Th17 mediated processes. In a first clinical trial, Brodalumab, which blocks IL-17 signalling by inhibiting the IL-17 A receptor, did not improve Asthma Control Questionnaire (ACQ) scores (primary endpoint) in a group of moderate to severe asthmatics[149]. Treatment did have beneficial effects in a subgroup with high reversibility to salbutamol although this finding was not confirmed in a subsequent unpublished phase 3 trial. A selective beneficial effect in bronchodilator responsive patients with severe asthma has also been reported with the TNF-α antagonist Golimumab, although this treatment was not pursued as there was a high incidence of malignancy in the treated population[150]. Patient selection was not optimal in

either the Golimumab or Brodalumab study as the presence of neutrophilic airway inflammation was not confirmed and markers of TNF-α[151] or IL-17 involvement were not included as criteria for patient selection. It remains possible that there is a definable sub-group of patients with severe asthma who derive net benefit from one or both of these treatments.

Airway infection/impaired airway defences

There is little doubt that viral infections are an important trigger for acute severe asthma and growing evidence of an abnormal airway response to infecting respiratory viruses resulting in an amplified airway inflammatory response and worse clinical consequences[152,153]. Challengingly, bacterial as well as viral infection has been shown to be present in acute asthma attacks[154]. Both are potentially identifiable and are therefore candidate treatable traits in patients with 'asthma' and there is existing evidence of efficacy of inhaled interferon-β in patients with severe asthma[88]. However, before we rush to antibiotic therapy for attacks, it should be noted that an equally plausible reason for positive bacterial cultures is transient, viral-induced topical immunosuppression.

Altered cough reflex sensitivity and efficacy

Cough is clearly an important airway defence mechanism, and the best treatment is to remove the underlying cause. There are significant age-related changes 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 are receiving high intensity treatment with little or no evidence of benefit[155]; little is known about the extent to which this is a factor in children. Adult patients are usually middle aged females presenting with a persistent dry cough associated with a heightened cough reflex, often in the absence of other features of airway disease[155]. Only a small proportion of patients have cough reflex hypersensitivity secondary to treatable eosinophilic airway inflammation[156]. Other treatable causes include cough secondary to angiotensin converting enzyme inhibitor treatment; however, a significant proportion has no obvious cause[155]. This component of airway disease is recognisable and quantifiable[155]; it is an important area for new research and for new drug development and there are encouraging signs of progress[157]. Similarly, reduced sensitivity or effectiveness of the cough reflex, related for example to medication or neuromuscular disease respectively, could theoretically be treated with cough augmentation techniques.

Conclusions

We acknowledge that it may not be possible to determine all the facets of airway disease in every patient, especially children, but the potential complexities should at least be appreciated.

Spirometry is difficult for young children to perform and it may not be sensitive enough to detect important abnormalities in some patients[158], but other reliable lung function techniques exist, which are less dependent on cooperation by toddlers and infants and may be more sensitive[159,160]. Lower airway inflammation can only be assessed in severe cases as bronchoscopy is not justified in most children with asthma. Measures in nasal secretions and breathomics 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. It is also clearly impractical to go through this mantra in patients with mild airway disease where there is little diagnostic doubt, for example in primary care in particular; the adult or child with an airway disease that is completely responsive to low dose ICS will clearly not want to submit to multiple airway tests! It is also clear that they are not separate discrete entities; for example, chronic airway bacterial infection may lead to neutrophilic inflammation and increased airway secretory products. It is obviously of particular importance to give heed to the currently treatable manifestations of airway disease whilst not losing sight of the need to develop novel therapies for currently intractable issues. Finally, we need to remember that some or all of these traits may have implications in the time domain as well as immediately, specifically conferring future risk even despite there being no apparent immediate harm. This has important implications, which we will discuss in a later section.

Precision management

"And Socrates said 'he who first gave names and gave them according to his conception of the things which they signified; if his conception was erroneous, shall we not be deceived by him?'"

Richard Asher taught that we still muddle up clinical observations and pathology, and name entities in a muddled way, leading to muddled thinking[161]. This is EXACTLY what has happened with the term 'asthma', where guidelines have conflated symptoms (cough, wheeze, and breathlessness), physiology (variable airflow obstruction) and pathology (eosinophilic airway inflammation). So we must describe what we see, using the framework in table 4 as at least a starting basis, acknowledge the gaps in what we know, and use terminology to illuminate not obscure. So asthma becomes a syndrome, and a diagnosis for a given individual should now become (say) 'an airway disease/asthma syndrome characterised by fixed and variable airflow obstruction but no eosinophilic airway inflammation or chronic infection' where high dose ICS will not be prescribed and future risk will be quantified and modified where possible. In the future, perhaps we will be able to say 'an asthma syndrome characterised by mutations in the IL-X pathway leading to excessive neutrophil

chemotaxis in response to pollutants, with secondary structural airway changes' and prescribe an anti-IL-X monoclonal antibody if we cannot remove the underlying cause.

Until then we have the traits of the asthma syndrome discussed above and in table 4. These at least have the merits of being linked to morbidity, and some at least are reasonably well defined, measureable, associated with morbidity and linked to specific treatment responses. We recommend these traits are used to structure an alternative approach to assessment and management, along the lines recently suggested by Agusti and colleagues[118].

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

This strategy recognising 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 given patient and may change over time, either as a part of the natural history of the disease and/or as a consequence of therapy. Importantly there is no assumption of a causal link between one component and another. The strategy encompasses overlapping disorders, comorbidities, environmental and life style 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 approach and we would hope they are refined and more specifically targeted to more clinically important mechanisms with time. So, with the advent of ever more monoclonals, we need

to move beyond cell based definitions to pathway based definitions, particularly in non-eosinophilic airway diseases. Although not definitive, there is already consistent evidence that the sort 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[10,11,24,25,162,163]. Additional strengths of this proposal are[118]:

(1) specific diagnostic criteria for the components are proposed, and expected treatment benefits outlines, in terms of patient relevant and surrogate outcome measures (Table 4-6);
(2) it recognises that different components relate particularly to different aspects of the clinical problem or future risks (i.e. eosinophilic airway inflammation and the risk of attacks);
(3) it may be cost-effective because of more economical use of treatment and the expected larger therapeutic response;
(4) it can stimulate best translational research by identifying knowledge gaps;
(5) it can help to identify key inclusion- exclusion criteria for future randomized clinical trials.
(6) it can be applied in any patient with airway disease leading to more precise therapy, rather than label and one size fits all approaches;
(7) it 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.

SECTION 2: BEYOND GUIDELINES. OPERATIONALISING INDIVIDUALISED TREATMENT IN DIFFERENT HEALTH CARE SETTINGS

Where are we now?

The rise and fall of guidelines

The paradigm for the management of asthma, hallowed by numerous international guidelines, is a one size fits all stepwise approach according to the level of asthma control (figure 5). This basic construct has not changed much since the first guidelines were published 27 years ago[14-17]. Current treatment is initiated with an inhaled SABA as required in intermittent asthma, with the addition of maintenance low dose ICS in mild persistent asthma, and then stepping up to combination ICS/LABA therapy in moderate asthma, with the dose of ICS in the combination inhaler increased in severe asthma to obtain control. This control-based management approach means that treatment 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 stepped care works well when dealing with a homogeneous well-defined condition, when treatment responses are relatively consistent between patients and across different outcomes, and when the goals of management are realistic and achievable; and indeed for many patients guidelines stressing anti-inflammatory therapy have brought substantial benefits. However, as is apparent from the sections above, neither of the first two criteria are met in the whole gamut of 'asthma'. Perhaps we have jumped headlong into the guideline production business without establishing first whether the entity whose management we are seeking to guide is useful and sufficiently well defined[22]. An additional problem is that the goal of treatment – to eliminate symptoms and attacks and to normalise lung function – may well be unachievable in a significant proportion of patients[164,165]. One result of this is to drive treatment requirements (and cost) up in a spiralling manner.

The providence, scope and proliferation of modern guidelines have all led to problems. By necessity guidelines result in recommendations that are conservative and based on evidence from randomised controlled trials carried out in well-defined but poorly generalisable populations[166] Treatment decisions at different steps are over-generalised, resulting in illogical treatment in significant numbers of patients. For example, the addition of LABA is recommended in patients whose condition is uncontrolled by low dose ICS, yet is this the best option for a patient who has evidence of active eosinophilic airway inflammation and whose dominant clinical problem is recurrent attacks? What is needed is to identify those patients who do not respond to the initial approaches suggested in figure 5 and below and move on to precision medicine rather than blindly following the standard step-up treatment plan. Early asthma guidelines produced evidence on a few core concerns for diagnosing and treating the condition. We have since seen lengthening of guidelines resulting in important recommendations being lost amongst minor self-evident ones. Increasingly guidelines are used to establish medical and legal standards of care resulting in recommendations that become set in stone, making it difficult to innovate and generate new evidence. Finally, a profusion of different guideline groups have emerged over the last 20 years leading, in some cases, to variable recommendations. Box 5 summarises the views of a number of influential guidelines on the use of FeNO to guide diagnosis and management of asthma. This conflicting and confusing advice occurs because different questions were asked. The 2016 GINA[87] and 2014 BTS/SIGN[167] paediatric guideline groups asked: how valuable is FeNO in supporting a diagnosis of asthma? They correctly concluded that it was not helpful. In contrast the 2014 BTS/SIGN[167] adult and 2011 ATS clinical practice guideline[168] groups came to a very different conclusion in response to a more

specific question which did not pre-suppose that 'asthma' was a useful entity: which test best identifies eosinophilic airway inflammation and corticosteroid responsive airway disease?

Asthma management in low and middle income countries

Poor precision of treatment and spiralling treatment costs are an important issue in low and middle income countries (LMIC) where tools required for diagnosis and effective inhaled therapies are routinely unavailable and/or unaffordable. Simple tests such as spirometry may have more utility in this setting as diagnostic overlap with respiratory infections or other chronic respiratory diseases occurs more commonly. Poor availability may therefore be a factor leading to diagnostic error and potentially under diagnosis. There is a lack of implementation of what would be regarded as standard care in high income places. The unacceptable inequity that still exists globally regarding asthma diagnosis and management and the collision of two worlds – in one where talk is about precision medicine and need for individualised phenotyping to guide diagnosis and management and in the other where there are not even basic tools for diagnosis and management – presents considerable challenges. We need to keep in mind that the predominant childhood population and a substantial adult population is in LMICs, so addressing the challenges of diagnosis and management in these settings will have a large impact, and if inhaled beclomethasone, inhaled salbutamol, prednisolone and a milk bottle spacer were available to all, the global impact would be huge[169].

Where do we want to go?

Move from one size fits all management to precision medicine

First and foremost, we need new approaches which deconstruct airway disease in all those who do not respond to the initial treatment recommendation. The key limitation inherent to the paradigm of the 'one size fits all' guideline-based approach to asthma management, based on ICS and beta 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[72,81] (table 4), and so a precision approach would seem more logical. For example, this may avoid both inappropriate 'overdosing' of ICS in symptomatic patients with non-eosinophilic asthma, including the obesity-related phenotype[23,115], inappropriate 'undertreatment' with ICS in patients with severe eosinophilic asthma, as well as inappropriate overdosing with maintenance LABA therapy in asymptomatic patients with relatively fixed airflow obstruction.

The precision approach we advocate addresses the increasingly recognised conundrum regarding the treatment of patients with the poorly defined asthma/COPD overlap syndrome, in which undue emphasis on the COPD component could lead to risks of sole bronchodilator LABA and/or long acting anti-muscarinic (LAMA) therapy, or undue emphasis on the asthma component which may lead to unnecessary side effects from ICS therapy and inadequate bronchodilator therapy. This problem (and the ACOS and COPD acronyms) disappears if the airway disease in the individual patient is deconstructed, and treatable traits treated, without worrying about diagnostic silos.

A related issue is whether alternative treatments to ICS and β_2-agonists may be preferable in selected patients. Specific 'responder' groups have not been identified for established treatments such as Theophylline, leukotriene receptor antagonists (LTRA) and LAMA, or potential treatments directed against latent infection or anti-oxidant stress. The further investigation of pathways and hence biomarkers to identify responder groups to therapeutic agents similar to the approach used with ICS 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 that make up the spectrum of asthma (see section 4).

Smarter monitoring and new treatment paradigms

Recommendations regarding monitoring of the asthma patients are unfortunately often also of the 'one size fits all' type. Should the monitoring approach be tailored to the specific phenotype of the patient? Monitoring should be considered as an iterative and adaptive process, whereby changes in the phenotype, drug response, adherence, developmental aspects in children and disease stability are constantly re-assessed (see figure 6). Patient's individual behaviour in the past should be considered by the physician for treatment decision making.

Once established on treatment, monitoring is an iterative process where symptoms and risk of adverse outcomes (i.e. attacks) are assessed and management fine-tuned. As symptoms due to airflow limitation and risk as a result of active eosinophilic airway inflammation are currently by far the most important and recognisable treatable components in patients with airway disease, the schema set out in figure 6 would be sufficient in most circumstances and should be applicable in primary care and other non-specialist settings[170]. 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 discussed in tables 4-6. Two immediately obvious scenarios are the patient with symptoms not due to airflow limitation and a patient with recurrent

exacerbations with low biomarkers of eosinophilic airway inflammation. Cough reflex hypersensitivity is an important cause of the former and infection-related neutrophilic airway inflammation of the latter. One advantage of the approach outlined above and in figure 6 is that these possibilities become apparent early on in the diagnostic process rather than after many months of fruitless and escalating inhaled treatment.

Several randomised controlled trials have shown that the precision medicine and smarter monitoring approach in adult asthma outlined above is superior to conventional stepped therapy in well-resourced countries[10,11,24,25]. In LMICs, the first priority is to get basic therapy available in every community (figure 5). When this has been achieved, we suggest that the approach illustrated in figure 6 is likely also to be useful although could be adapted to this setting. It should be noted that our proposed approach does not make the assumption that asthma in Africa is the same as in London; indeed, given the much greater and more disparate burden of childhood infections in LMICs, they may be very different[171,172]. This is another problem in the use of umbrella terms across the globe; it is so easy to slip into the assumption without even noticing this has happened. For example that the disease is the same in Paris and Paraguay, and that what works in Paris should be uncritically deployed in Paraguay

There are, however, several important unresolved issues. One key question is how 'stable' are the eosinophilic and non-eosinophilic asthma phenotypes and whether simple biomarker assessments (e.g. blood eosinophil and FeNO, which are predictive of a response to ICS) will consistently identify these groups[173]. The related clinical question is whether ICS can be safely withheld in patients with a specific biomarker profile. This highlights a key feature of the proposed paradigm: the need for stratification in planning treatment. Some patients with objectively documented episodic asthma may be eosinophilic at one point but not at another[174] but it might be difficult to distinguish true 'episodic asthma' and 'episodic symptoms with unrecognized persistent airflow limitation or inflammation' without repeated objective evaluation. Overestimation of control and difficulty understanding symptom patterns over time might present additional difficulties, particularly in paediatric care, where the history is primarily obtained from a third-party (parents) or reported by children. The pragmatic solution may be to use intermittent and/or regular low dose ICS/SABA or fast onset LABA/ICS combination therapy in such patients as discussed below.

The second key question is what to use instead of escalating doses of ICS in patients with non-eosinophilic obstructive airway disease. LABA monotherapy has been shown to increase the risk of

mortality in patients with asthma[175]. Whilst it may well be the case that this risk is exclusive to patients with an eosinophilic pattern of disease, it would be difficult to prove this definitively. We therefore suggest that as required ICS/SABA or fast onset LABA/ICS combination therapy is the default position in patients with variable symptoms and/or airflow limitation, but that ICS dose is not escalated unless biomarkers of eosinophilic airway inflammation are raised (figure 6). Long-term low dose macrolide antibiotics have been shown to be effective in small studies of non-eosinophilic asthma[141,142], but patient side effects and concerns about global antibiotic resistance limit their widespread use. The use of alternative treatments such as Theophylline, LTRA and LAMA has not been examined in detail in this patient group so it is difficult to make specific recommendations. The weakness of all these suggestions is that they lack a satisfactory evidence base; we urgently need to understand pathophysiology and pathways as a basis for management approaches which are assessed in RCTs, if we are going to offer these patients 21st century care rather than firing treatments at them with the current scattergun approach.

Crucial to the current approach is the validity of the 'cut-points' at which prescribers and patients move up or down to the next step in treatment. Arguably the most important step is when low dose ICS are prescribed, a therapeutic approach which previous guidelines have recommended when patients use their SABA on more than two occasions per week[86], and more recently (based on growing evidence), on two or more occasions per month[87,176]. However, international surveys have shown that doctors do not recognise the need for ICS therapy at such stages[177] and there is a tendency for patients and clinicians to overestimate control. Furthermore, if prescribed, adherence to ICS may be as low as 20%, which is not surprising as patients are required to take twice daily treatment regardless of whether they have symptoms[178]. Recognition by primary care practitioners that patients with intermittent and/or mild asthma are unlikely to be adherent with regular ICS treatment may make them reluctant to issue a prescription. However, poor adherence is associated with significant asthma-related morbidity, and there is a greater than three-fold increased risk of an asthma exacerbation after stopping low dose ICS[179].

Recognition of this conundrum has led to consideration of methods that are applicable in primary care, which may improve ICS adherence, as well as alternative regimens to that of sole SABA therapy for symptomatic relief in intermittent asthma. The biomarker directed approach suggested in figure 6 might help clinicians to make a definitive treatment decision and encourage patients to commit to that treatment. The current first step is use of SABA as required; this is only logical if what is treated is intermittent constriction of airway smooth muscle. If in fact there is concomitant, albeit low-grade

eosinophilic inflammation, should this not also be treated, perhaps using a combination ICS/fast-onset β_2- agonist inhaler solely as reliever therapy? Stated in these terms, the absurdity of the current debate between these two options as step 1 is manifest; what is needed is not a sterile debate about possibilities, but measurements of the problem and precise treatment, even for apparently mild disease. There is a substantial rationale for a regimen that utilises symptom-driven β_2-agonist use as the vehicle for ICS delivery and allows self-titration of ICS dose according to changes in asthma control[9]. However, this approach (as do so many current paradigms) 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 in adults with intermittent and mild asthma has shown that the symptom-driven use of combination ICS/SABA medication achieves similar efficacy to regular ICS therapy, and leads to fewer severe exacerbations compared with sole SABA reliever therapy[180]. In children, the TREXA study showed that, in the phase of weaning down treatment, intermittent combined ICS/SABA were more effective than SABA alone, and had fewer side-effects than continuous low-dose ICS albeit at the expense of slightly lower lung function[181]. As there is no place for treatment with LABA monotherapy in asthma (perhaps particularly in those with eosinophilic airway inflammation), we should question the use of SABA monotherapy in mild asthma of this phenotype. Further investigation of ICS/SABA and ICS/fast-onset LABA reliever therapy for intermittent and mild asthma represents a priority and will determine whether single inhaler therapy may be possible across the spectrum of asthma severity, initially with a single ICS/fast-acting β_2-agonist inhaler used as reliever therapy only, then progressing to its use as both maintenance and reliever therapy (MART).

From a therapeutic perspective, ICS/fast-onset LABA therapy prescribed according to the maintenance and reliever regimen reduces the risk of severe attacks by about 40 to 50% compared with prescribed maintenance ICS/LABA and SABA reliever therapy, despite similar efficacy for other outcome measures such as lung function and asthma control[182,183]. Efficacy of this approach, and of a biomarker directed approach, is particularly obvious during times when the risk of attacks is increased[184] and perhaps in poorly adherent patients[185]. This evidence underlies the preferred use of ICS/fast-onset β_2-agonist therapy (prescribed as needed or according to the MART regimen) in patients requiring therapy for documented episodic disease. Since the MART approach is based upon the hypothesis that an increase in asthma symptoms is due to increased eosinophilic airway inflammation, which responds well to additional doses of ICS within the ICS/fast-onset LABA reliever, this approach may be most applicable in patients with eosinophilic asthma. However, it would be

difficult to identify with confidence a population of patients in whom ICS can be safely withheld and we believe that it would be reasonable to adopt this approach generally.

Better appreciation of the dose-response relationship with ICS

There is also a need to revise the current guidelines classification of low, moderate and high daily doses of ICS. In adults the current classification that low doses are represented by fluticasone propionate (FP) doses of 100 to 250µg per day is not based on evidence that 90% of the maximum obtainable therapeutic benefit is achieved at an FP dose of 250µg per day[186], or the lack of greater efficacy with initiation of ICS therapy at daily doses above 400µg budesonide or equivalent[187]. In children, the BADGER study showed that few improved when the dose of FP was increased above 100 µg bd[188]. Further investigation of the ICS dose-response relationship for both efficacy and systemic adverse effects is required, particularly in children. However, there needs to be an appreciation that this plateau may well be dynamic. So if there is a considerable pro-inflammatory drive - for example from exposure to aeroallergens to which the patient is sensitized and cannot avoid - then there may be relative steroid resistance leading to the requirement for larger and more frequent doses of ICS [189]. This underscores the value of the approach described in section 1 to not consider airway disease in isolation, but also in the context of the environment. Interestingly, systemic absorption of high dose ICS is less in those with inflamed airways[190], which may 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 may be so high that small changes in recruitment signals in the airway, or the involvement of novel pathways not inhibited by ICS, lead to important worsening of airway inflammation. This possibility is supported by the beneficial effects of depletion of circulating eosinophils with anti-IL-5, and the very close relationship between clinical benefit of treatment and the pre-treatment blood, but not sputum, eosinophil count[12]. If this model is correct then it is not inconceivable that any benefit of very high dose ICS is a direct result of systemic activity and 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 proper use of medication delivery devices and adherence. In this context, the continued, widespread use of metered dose inhalers without spacers is a manifestation of truly impressive complacency, given 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 (less than 3 years), the elderly with coordination

problems, those who need high doses of ICS (likely far fewer numbers than those prescribed them!) and possibly in LMIC settings for financial reasons, a case can be made to ensure universal use through their modification so that they can only be activated when attached to a spacer. If adherence is to be tackled, we need to have devices that detect not merely activation but also inhalation and its adequacy, and feed this back day by day to the patient and the physician, with alerts when medication is not taken. We need research to better understand patients' responses to these devices and this type of monitoring. Futuristic? The Hubble telescope can beam images from the edge of the known universe down to earth, and yet those of us treating a life-threatening disease are content to use old-fashioned technology to deliver medications. It is salutary to reflect on the differences between the Bakelite dial telephone of twenty five years ago and the modern Smartphone, during which time progress in metered dose inhaler technology has been exactly zero. Small wonder that we do not use the medications we have effectively!

Although we argue against individual therapeutic trials as a basis for long-term treatment decisions, it is an unpalatable fact that currently these are inevitable in at least some contexts, e.g. pre-school wheeze. However, we can progress beyond giving an inhaler and asking if it worked after a six-week trial. There is no reason why these N-of-1 trials cannot be placebo controlled, double blind and incorporate electronic monitoring of adherence, including technical adequacy of the inhalation technique.

21st century asthma clinics

Finally, in considering asthma management in its broader context, ways to enhance the patient/healthcare 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[87]. One of the important concepts of asthma 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, out-patient consultations have not changed in over a century; an unruly scrum waiting to be seen, a brief face to face consultation with someone with a medical degree and variable knowledge of the patient and the disease, who may or may not have access to the previous notes, then summary ejection until it is time for the cycle to repeat itself. The challenge now exists to utilise advances in information technology and communication, which have been underutilised in the past, to improve such partnerships in an evidence-based and cost-effective manner. The young use social media to communicate many times a day; why do we not use this in

health care? It is possible to use a smartphone APP to monitor how many steps someone has walked in a day; why do we not use APPs to monitor airway disease continuously and in real time, obviating the need for patients to perceive symptoms? There is already evidence that this sort of approach works[191] and even in LMICs, many have smartphones – can these not be utilised to improve access to health care?

SECTION 3: WHEEZING ILLNESSES ACROSS THE AGES

Where are we now?

The evolution of airway function between the first and tenth decade has been described by curves produced from nearly 100,000 cross-sectional observations. It is clear from these and other data that there are three key places that can impact on long-term risk of airways disease. The first is to ensure normal lung function at birth - abnormal birth (or at least, pre-school) lung function tracks into the third decade at least; the second is to ensure normal growth in lung function during childhood until to a plateau is reached at age 20-25; and the third is after this age, when accelerated decline leads to low lung function in later life.

A large number of overlapping birth and other cohorts have been studied, in some cases with follow up over many decades. These have taught us that, in chronological not discovery order:

- Transgenerational factors (grandparental smoking) impact on risk of airway disease[127]
- Antenatal factors such as exposure to tobacco smoke[135] and pollution[133] impact airway disease in the foetus in three main ways: (a) by an effect on gestational age and birth weight; (b) by direct effects on lung structure; and (c) by effects on the foetal immune system leading to abnormal responses to allergens and viruses[134]
- Place (home vs. hospital[192]) and mode (vaginal vs. Caesarian section[56]) of delivery may impact the risk of future airway disease
- In the immediate post-natal period, there is further loss of lung function in those who develop persistent wheezing illnesses, in particular if there is neonatal airway hyper-responsiveness[59]
- 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[63,193,194].

- Postnatally, passive smoking[55], pollution[133], moisture damage[195], obesity[196], pesticide exposure[197] and multiple early atopic sensitization[64,66] 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 later COPD[126].
- Spirometry tracks over many decades; under most circumstances there is no catch-up lung growth[129]
- Airway disease in pre-schoolers may recrudesce after quiescence in adulthood or manifest for the first time in adulthood[50]
- Adolescent girls with premature menarche may have an increased risk of developing asthma[198].
- There appear to be multiple trajectories to 'COPD'. In a recent longitudinal analysis showed that of those with an FEV1 is $\geq$ 80% in early adult life, 158/2207 (7%) had a fast decline in spirometry and developed COPD. Another group had a FEV1 < 80% in early adult life, and 174/657 (26%) developed COPD; they had normal rates of decline in spirometry. Both trajectories contributed equally to the burden of COPD, although clearly they differ in the rate of decline in lung function in later life[129]. Subsequently, follow up of the CAMP study bridged the gap between adult and childhood studies[199]. There were four asthma spirometry trajectories, comprising combinations of normal or reduced plateau of lung growth, and normal or early decline in spirometry, independent of treatment prescribed (nedocromil, budesonide, placebo).
- In the many large studies of rate of change of spirometry in adult life[200-203] no single environmental factor, including smoking, consistently predicts an accelerated decline.

In early life, we must move on from irrelevant questions like 'at what age can we diagnose asthma?' (which, as we argue above, is neither a single diagnosis nor an intelligent question) and instead, think about the treatable traits of airway disease[53]. So in early life, we still quarrel about what is bronchiolitis and what is viral wheeze, and what is asthma without defining our terms clearly, and worse still, have no biomarkers to differentiate them. We know that viruses are an important trigger of attacks of wheeze[152,153], but we have assumed that all viruses are equal, and equally treatment resistant, on the basis of limited data[204]. We know that children with eosinophilic airway inflammation and variable airflow obstruction at school age had airflow obstruction at birth and/or during early life[59]; but other than tackling tobacco smoke and pollution (in a half-hearted manner) we don't know how to prevent this. We know that aeroallergen sensitization (in particular, multiple early sensitization) in the same time period is associated with ongoing symptoms and loss of lung

function and persistent airway hyperresponsiveness[64], but we don't know how to prevent this either, this despite knowing that airway function tracks from the pre-school years to late middle age, so the pre-school years are critical. We cannot prevent early viral infections like Rhinovirus or Respiratory Syncytial Virus (RSV) in most children, and current work on the development of anti-RSV approaches has produced mixed results[205,206]. We have also become bogged down in irrelevant questions like 'do children with sickle cell disease/bronchopulmonary dysplasia/other causes of wheeze have 'asthma', instead of trying to determine the specific nature of their airway disease in terms of the traits shown in table 4.

Current knowledge of the developmental trajectories of asthma is limited. A number of prospective cohorts have established patterns of wheezing going forward from infancy; and largely from a series of overlapping cohorts, the significance of early wheeze has been determined in adult life (see above). However, these studies are in large populations, and by definition are non-invasive, and hence tell us little or nothing about the developmental changes in mechanisms. For example, the assumption is made that atopy-associated asthma in school age is driven by the same pathways as in adults; but there is at least some evidence that in severe asthma, the innate epithelial cytokines and lineage negative innate lymphoid cells may be more important in severe asthma in children than in adults[207]. Furthermore, classical adult asthma phenotypes and complications (aspirin sensitive asthma, allergic bronchopulmonary aspergillosis, occupational asthma, late onset asthma) remain in adult silos, with largely very little attempt to understand whether they have their roots early on; this despite the clear demonstration[208] that women with so-called 'late-onset asthma' actually had significant symptoms (long forgotten) and physiological abnormalities in early life! Indeed the very term 'late-onset' pre-judges the issue, and discourages any thinking about probable early roots.

We know that recall of even major childhood respiratory illnesses (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 adult life interviews[208,209]. In the context of interstitial lung disease, we can clearly see that the same gene mutation (SpC) in the same kindred can cause very different diseases (neonatal pulmonary alveolar proteinosis[210], adult onset pulmonary fibrosis[211]), presumably related to modifier genes and environmental exposures. There is animal evidence that transient exposures during key time windows (e.g. neonatal hyperoxia[212]) may affect responses to allergens and viruses in adult life. So it is at least conceivable that some of the adult phenotypes which we think we do not see in childhood are in fact manifestations of something causing a very different early airway disease. These age windows may be a key opportunity for

disease modifying treatment or primary prevention strategies. It is highly unlikely that there will ever be a big enough birth cohort to study these relatively uncommon adult phenotypes prospectively, (and even if one is started, it will only be of interest to our professional grandchildren) so a different approach will be needed.

The evolving picture of airway disease is characterized 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, if they exist, are as yet unknown. Li et al[213] have postulated that small risks may 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 given risk allele might be magnified by an adult life exposure, for example occupational, or become relevant during lung aging, for example impaired pre-school airway development.

The development of the respiratory system in early childhood is complicated, however, by growth processes and adaptation to changing environments, including going from intra-uterine to extra-uterine. Complexities also occur in the aging adult as a result of age-related senescence. While some outcomes may be the result of a cumulative effect, complexity theory suggests that these mechanisms and interactions are likely far more complex, non-linear, and they remain not merely largely unknown, but not even considered. Interactions can only be hypothesized based on general principles inherent in complex systems biology, such as degeneracy[214]. Degeneracy in systems biology refers to the ability of alternate structural pathways to exhibit similar or dissimilar functional outcomes depending on context. Frequently mislabelled redundancy, degeneracy refers to structural variation whereas redundancy refers to structural duplication. Degeneracy has been described in the immune system[215], the control of breathing[216], and human movement analysis[217]. For adaptive, complex systems, degeneracy has several benefits - e.g. it improves robustness to perturbation by, for example, an environmental stimulus and allows for adaptability[218]. In the developing respiratory system, complex behavioural adaptations may be necessary in order to adapt to changing environmental conditions from foetus to adulthood. Given such phenomena, the overall asthma risks may 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 may have contributed to the evolution of a greater heterogeneity of phenotypes than has previously been considered, given 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 7 shows recognised wheezing syndromes by age, with suggested major treatable traits. Machine learning approaches have been fruitfully applied to the study of atopy[67,219], once considered an 'all or none' phenomenon. In fact, only the latent class of early multiple atopic sensitization (but not any other sensitisation classes) in the Manchester and Isle of Wight studies[67,219] was associated with a worse trajectory of lung function, in particular if associated with acute attacks of wheezing[51]. It is very clear that the complexities of asthma trajectories cannot be described in simple terms, or by single cross-sectional measurements, and that conclusions drawn from cross-sectional analyses of longitudinal data may not accurately reflect longitudinal trajectories within individuals[220]. Moreover, while 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 may or may not apparently resolve), and in others health is maintained. It is likely that several sub-systems are involved in this complex disease, interacting in a network-type manner. These sub-systems or "compartments" include, 'lung growth and structure', 'innate immunity' (viral infections, mucociliary clearance, surfactant, toll-like receptors, etc.) and 'adaptive immunity' (IgE/G_4; response to infections), 'allergic sensitization', 'epithelial function (barrier and secretory)', 'oxidative stress response', 'remodeling and repair mechanism', 'smooth muscle function', 'metabolic rate and nutrition', 'interaction with the microbiome', and many others.

Notably, all of these compartments are influenced by specific genomic and epigenomic regulators, and are similarly altered by environmental factors which may be specific to that compartment[221]. Genomic and epigenomic changes have not only been associated with atopy and asthma, but also amongst other factor with airway smooth muscle function, lung function, glucocorticosteroid response, effects of prenatal tobacco exposure, air pollution, prenatal sensitization, stress[222] and viral infections[223]. Based on these considerations, future asthma models need to consider not only developmental gene-environment interactions of the organism, but also those of each compartment, as well as 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 given polymorphism may be age-dependent and be different with different environmental exposures[65]. Gene expression and epigenetic regulation change by age, and can even be induced during pregnancy[224]. The relative importance of innate and adaptive immune response drastically changes in the first year of life in response to environmental antigens and also in the context of asthma[63,225,226].

The dominant maturational changes in each compartment or subsystem of the body take place at different times. For example, airway size and lung volumes increase until adolescence, whereas the development of the immune system, or the stabilization of the gut microbiome[227], is complete in early childhood (Hypothesis 1: Figure 8). Consequently, if asthma is considered a network response of many weak effects in all of these compartments, their relative contribution, or their susceptibility to environmental stimuli, likely also changes with age (Hypothesis 2: Figure 9). Age-dependent effects of risk factors on respiratory symptoms has have been demonstrated, for example, in the case of tobacco smoke exposure[228], immigration studies[229] and farming exposure[230]. Maturational programming is likely to be determined by the interactions between intrinsic (e.g. growth processes) and extrinsic factors. The system adapts, 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 result is the given compartment 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 recent model has suggested that the gene-environment interaction determines the asthma phenotype in early childhood[231]. It is likely that the relative contribution of a specific compartment could become dominant at a given age, and could determine the phenotype. Our hypothesis (Hypothesis 3: Figure 10) is that the evolution of asthma may be an aberration of one or many different interacting compartments. The compartments involved in the transient wheezing phenotype may include, among others, airway size and innate response to viral infections. In contrast, persistent wheeze may be an early aberrant stabilization in response to disease, which may impede subsequent healthy maturation. Intermittent phenotypes may manifest as changing states of stability in response to environmental exposures or unrecognised persistent disease between attacks.

Where do we want to go?

Cross-sectional studies cannot study asthma disease trajectories. Future studies would thus need to assess key compartments of the disease process with a multi-dimensional or even multi-level (gene-molecule-cell-organ) approach, as well as the interaction between them and quantify their relative contributions. We need to know how the genes and environmental factors affect the key compartments that lead to cumulative or even critical effects in the context of development. Such network type analyses are well known in systems biology. We thus need a step change in longitudinal studies, using well-defined outcomes reflecting the various compartments (lung function, immunological, inflammatory, metabolic, genetic, epigenetic). Furthermore, systems medicine often neglects the idea 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, it is critically important to quantify and characterize the individual's response to the exposome (i.e. every exposure to which an individual is subjected from conception to death)[232]. This is an example where if paediatricians emerge from their silo, they can learn a lot from adult Occupational Health physicians.

Clearly even if a new birth cohort study addressing 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! So we need to use existing longitudinal and also cross-sectional studies innovatively. For example, a detailed biological signature of the rapid decliners in adult life[129] should be compared with the same parameters earlier in life, to determine whether this group can be detected early, at a time when (perhaps) an intervention can abort later deterioriation. One example is serum CC16, which is associated with reduced lung function in childhood, and accelerated lung function decline in adulthood[233]. This can be a two way process – are early biological phenotypes and signatures associated with later phenotypes? So some cohorts had no early microbiome studies, but they could obtain late middle age samples, which could be compared with those of cohorts in childhood and early adult life, as well as being explored in animal models. This is not the scientific ideal, but until time travel becomes an option, it is a pragmatic approach to understanding longitudinal biological complexity.

To develop preventive strategies we have first to understand the pathways whereby early life events effect lung function in the long term. We need to identify factors that prevent or reverse adverse changes, and the understanding of normal lung development may be a prerequisite. Basic science could help by developing better animal models with long-term observations in the growing animal

and studies looking at the interactions of a multitude of small triggers, rather than single e.g. house dust mite exposures (see below); and epidemiologists and basic scientists need to emerge from their silos to co-design these models. These models need to use network-type analyses to assess the key compartments and pathways, their interactions and their relative contributions and how these result in cumulative or even critical effects during various phases of development.

If these ideas are correct, epidemiological studies need to be taken to a whole new level of complexity. 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 by environmental interactions, that is acceptable in big, longitudinal, population based studies. The challenge is also to mine existing cohorts for data that may be used to show insights into these complexities; in this context, the harmonization of cohorts into big data sets, such as the STELAR e-lab[234], are particularly welcome. We also should lift our eyes from a pulmonary focus, and consider whether other organs (e.g., the cardiovascular, endocrine, metabolic and/or neurologic systems) might have also suffered similar developmental abnormalities[235]. We know that trivial decrements in lung function and birth weight are associated with disproportionately increased mortality rates. Are they canaries in the mine for the whole body?

From a clinical perspective we have been blinkered into honing down onto the immediate disease manifestation, and failed to ask three basic questions:

- What was the developmental trajectory to the current status?
- What are the current components of the airway disease (section 1)?
- What will be the onward developmental trajectory from here?

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

SECTION 4: BEYOND PALLIATIVE CARE – TOWARDS PREVENTION AND CURE

Where are we now?

The standard answer to the question of what constitutes the greatest unmet need in asthma almost invariably highlights the requirement for more effective therapeutics for patients with chronic asthma who are refractory to currently available treatments. While this understandably resonates with treating physicians and their patients, its blanket acceptance as the number one priority across a wide segment of the asthma research community, and amongst drug developers, health care

providers and regulatory authorities, serves to perpetuate what has become the *status quo* in developed (and increasingly in developing) countries: the inexorable progression from intermittent early childhood wheeze to persistent asthma in the teen years, and thence to an ensuing life sentence of therapeutic drug dependence[236]. From a public health perspective the answer to the same question is of course radically different: "the lack 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 bear some responsibility for the low priority afforded to primary prevention strategies. By jumping straight to established asthma, and not considering the fundamental underlying causes, they have set the agenda for asthma as a disease to be controlled not cured, without apparently focussing on at least trying to devise strategies to intervene early to prevent progression to this state.

Hence it is unsurprising that disease control-based care has informed much so called 'innovation' in asthma. The focus has been on newer and more potent ICS and once daily LABAs, which can be characterised as merely more of the same. Do we really *need* another ICS? Should NICE and other regulatory authorities put a blanket ban on licensing any new ICS or LABA unless they are cheaper than and at least as effective as what we have already? We also need to be aware of the possibility that increasingly potent ICS may be harmful. The airway mucosa has and requires sophisticated immune defence mechanisms against pathogens and other inhaled irritants and ICS increase the risk of pneumonia, tuberculosis, and atypical *Mycobacterial* infection[103].

These new ICS have led to spiralling costs of asthma treatment which seem set to continue rising despite evidence of diminishing returns[19]. Are the newly formulated inhaled corticosteroids really any better than Beclomethasone? Some of us have argued before[236] that the continuation of this trend is inevitable unless there is a substantial realignment of entrenched drug development policy in the pharmaceutical industry and a parallel shift in licensing policy by regulatory authorities to encourage the development of drugs capable of halting 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[237]. What is needed is informed debate on the risks versus potential benefits of this approach.

Where do we want to go?

Absolutely key is the recognition that the pathways which initiate asthma and those that propagate established disease are entirely different; early on, cellular inflammation is absent[136], and ICS are ineffective[68,69]. We need to understand the early pathways in detail, so we can develop 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, the last two decades has witnessed the progressive accumulation of data on asthma development from foetal life through to early adulthood (see section 3). While many questions relating to asthma aetiology remain contested, these studies are more remarkable for the broad concordance in many of their findings relating to major asthma-promoting risk factors operative during early life, particularly in regard to the most frequently encountered atopic asthma phenotype. Prominent amongst these risk factors are lower respiratory tract infections and particular patterns of sensitization to aeroallergens, which can act either independently or (more importantly) act in concert to trigger episodic cycles of airways inflammation and accompanying wheezing symptoms[152]. The continued recurrence of these inflammatory events, particularly during the preschool years when postnatal lung growth rates are highest, appears to perturb normal maturation of respiratory functions, thus sowing the seeds for ensuing development of persistent asthma[237]. 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 symptom with persistently low airway function. Allergen immunotherapy is currently the sole truly disease-modifying treatment at our disposal; whereas the benefits of ICS are lost as soon as they are stopped, the benefit of three annual cycles of grass pollen immunotherapy on allergic rhinitis continued for years after cessation[238].

These findings provide a framework for the systematic testing of a range of therapeutic options relating to primary and secondary prevention, based on the selective targeting of these two interrelated risk factors (lower respiratory tract infections and particular patterns of sensitization to aeroallergens) that contribute significantly to susceptibility to airway symptoms in early life. In principle, inflammation resulting from the local activation of anti-microbial and/or atopic pathways arguably constitutes a plausible acute treatment target in infants and young children with recurrent airway symptoms; however, it is clear that ICS 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 the recent study of year-long treatment of at-

risk children with Omalizumab[239] 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 pre further schoolers. Moreover, the successful use of this agent on an autumn/winter-only basis for reduction of exacerbation frequency in asthmatic children[240] provides an illustration of how focusing specifically on known "high risk temporal windows" may also be used to further refine prophylactic treatment protocols. An additional example is the bacterial lysate immunomostimulatorOM85, which has been previously been used for attenuation of infection-associated episodic symptoms in adults with COPD[241] and in pre-schoolers with recurrent wheeze[242]: this has recently received regulatory and national funding agency approval in both the US (NCT02148796; https://clinicaltrials.gov/) and Australia (ACTRN12612000518864; www.anzctr.org.au) for use in preventive trials in infants related to later asthma development, and for use in Australia on a "winter treatment only" basis for prevention of exacerbations in school age children (ACTRN12614000062628 ; www.anzctr.org.au).

One difficulty in these and related trials is determining risk – the positive predictive value of many available indices are little better than flipping a coin, although negative prediction is very good[68,243,244]. It is clear that these predictive indices are based on the crudest markers; a recurring theme is that the respiratory community has by and large failed to rise to the challenge of using modern omics technology to determine predictive biomarkers (also a recurring theme of this Commission), although there has been some progress recently[245]. The first major initiative in this regard targeted prevention of allergic sensitization in high-risk infants by immune tolerance induction employing prophylactic allergen-specific sublingual immunotherapy, aiming to reduce ensuing asthma development by age 5-6 years. This trial was downgraded to pilot status after recruitment of only 50 children, enabling subsequent collection of safety data only[246]. However, it is noteworthy that a conceptually identical trial funded subsequently by the National Institute of Allergy and Infectious Diseases (NIAID) aimed at prevention of allergen-specific sensitization to food allergen by oral administration of tolerogenic doses of allergen has successfully achieved its primary endpoints[247], and a smaller sublingual tolerance induction trial in the UK funded by the Medical Research Council (MRC) targeting prevention of sensitization to aeroallergens has achieved partial success[248]. This approach clearly shows promise and should be systematically followed up. Encouragingly, a number of such studies are in 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[226]. The direct approach of specifically targeting the relevant pathogens is complicated by *inter alia* the broad spectrum of viral and bacterial agents potentially involved, that parts at least of the microbiome are important for early immune development and must be carefully preserved, the lack of relevant vaccines, and potential dangers of bacterial drug resistance associated with over-use of antibiotics. Attacking the problem via enhancement of the overall efficiency of developmentally compromised host defence mechanisms via the use of microbial-derived agents exemplified by pro-/pre-biotics has been widely discussed but at this stage the effect size of such treatments appears modest[249]. One issue likely related to this is the imprecision with which the contents of specific pro-/pre-biotics is known. Emerging data on the use in high risk infants and children 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 OM85, discussed above. Finally, early but important data on the effect of fish oil supplementation of the diet has, for the first time, provided compelling evidence of a positive effect on the natural history of childhood wheezing illnesses[250].

The single factor limiting progress in this potentially exciting area is the lack of relevant paediatric safety data. In this respect Omalizumab is a prime example. This effective biological treatment has been in use in adults for 15 years, and yet the necessary safety data in children under school age which would open up possibilities for primary prevention trials in high risk pre-schoolers is still not yet available. The range of potent and increasingly selective type-2 cytokine blockers available for adult asthmatics is growing rapidly[3,27-29], along with other relevant drug classes such as those targeting innate immunity[251], but there is little evidence of other than token interest on the part of drug manufacturers or the governmental agencies, which effectively set the drug development agenda, in changing the prevailing paradigms. Might a fast-track scheme be useful for moving some impressive drugs forward in paediatric severe asthma? For this to succeed, it would be important for paediatric investigators to contribute patients, which has been a problem in recent years[252].

We would have to conclude that the chances of committed researchers leveraging off these emerging advances in therapeutics for prophylactic purposes is depressingly remote. In this regard, federal legislation in the US dating to 1998 mandates that FDA play an active role in encouraging the manufacturers of existing and new drugs for the treatment of established asthma, to test the same drugs in early stage disease in childhood[253]. But there is no evidence of this mandate being effective.

As many researchers in this area can attest on the basis of personal experience from discussions with industry colleagues, business plans associated with release of new asthma drugs rarely include a serious paediatric component, and never include *prevention*. This will not change unless the clinical/research/regulatory communities become proactive in arguing this case more forcefully. This is a very crucial but delicate issue. Remission-inducing and curative strategies might require billions of dollars invested in clinical trials. Recent curative medicines have attracted price tags in the $US300000-1 million range. Will industry be ready to kill the 'cash-cow' of long-term palliative medications by funding studies which potentially will obviate their need?

So in summary, no more 'me too medicines' should be developed but real energy should be directed to going from control-based treatment to prevention or cure.

SECTION 5: ATTACKING ASTHMA ATTACKS

Where are we now?

It is important to be clear about terminology. Definitions vary and some events, such as episodes of increased symptoms and/or increased airflow limitation picked up on review of diary cards, have been identified as 'mild exacerbations' in some studies[81,254]. These episodes tend to be responsive to short acting beta agonists given for relief and are prevented by long-acting beta agonists whereas events leading to prescription of oral corticosteroids or hospital admission are less so[81,175], suggesting important differences in pathogenesis. There is evidence that a key difference is that more severe events (i.e. those resulting in unscheduled medical attention and/or unscheduled use of oral corticosteroids) are associated with loss of bronchodilator responsiveness and the presence of airway inflammation[255]. Events defined in this way have proved to be a robust outcome measure and are highly responsive to anti-inflammatory treatment. However, yet again we need objective biomarkers of different inflammatory patterns associated with deteriorations, and of their recovery, rather than 19th century, subjective approaches.

One consequence of not clearly discriminating loss of symptom control from genuine attacks has been that the inadequate word 'exacerbation' (or 'exasperation' as many patients understand it) has crept into our descriptions of acute asthma attacks. This 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 setting 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 the former have mortality rates and costs comparable to those of heart attacks[256]. CF lung attacks are associated with more rapid decline in lung function and increased risk of death or lung transplantation[257]. Repeated asthma attacks are also associated with a more rapid decline in lung function: in a post hoc analysis of the START study, in children and adults, but interestingly not adolescents, there was an accelerated decline in spirometry in those experiencing an asthma lung attack while on placebo, but not on budesonide[258]. Importantly, the protective effect of budesonide suggests that 'something CAN be done'. Whether the 'exacerbations' were related to poor adherence or the intrinsic severity of the disease is irrelevant to the question of whether 'lung attack' is a useful term. What is clear is that what has hitherto been called 'exacerbation' is not a temporary inconvenience, but a sign of a worse prognosis, which should call forth immediate action.

An additional problem related to the dissociation between symptoms/disordered airway function and the risk of asthma attacks discussed above is that it cannot be assumed that an asymptomatic patient with normal lung function is free of risk[259]. Current 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[260]. The recent UK national enquiry into asthma deaths identified, once again, that apparently low risk patients continue to die of asthma; the tragic absurdity of this concept is discussed below[78]. We need new management algorithms 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 in section 2. For this assessment we need to move beyond the airway, to extra-pulmonary and environmental/lifestyle factors[118]. We need to understand 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.

Finally, our 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[261,262]. The acute attack provides a unique opportunity to offer a root and branches review of the circumstances of the attack in a captive and potentially more receptive patient. Are we making the most of this opportunity? We know that patients admitted to hospital

with an acute attack have a poor prognosis and a high rate of requiring additional treatment, particularly in the short term[263]. Could we do more to prevent this happening? A first step might be an end to the prescription of a fixed term dose of oral corticosteroids with no follow up to assess response. Secondly, treatment protocols should mandate a re-assessment of all aspects of care to identify: (1) what went wrong and could it have been prevented; (2) was the response correct in terms of the treatment plan; and (3) should the treatment plan be altered with the wisdom of hindsight?

There is an even greater problem with 'wheeze attacks' in pre-school children. Here there is conflicting evidence that either corticosteroids[264-266] or leukotriene receptor antagonist therapy[267] reduces the risk of attacks or are useful in the treatment of attacks[196,268]. There is a huge need for effective therapies in this age group.

Where do we want to go?

Our limp response to 'exacerbation' is in stark contrast to the Cardiologists' focussed, highly effective and life changing response to a 'Heart attack'. We should emulate them. So:

1. 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. Patients and families need to know this.
2. A lung attack should prompt a full review of all aspects of the problem, including co-morbidities, management, adherence, adverse environmental factors and psychosocial issues, which must not be permitted to decline into a box-ticking exercise.
3. We must make the most of opportunities to prevent these episodes. In many countries there are high risk periods for asthma attacks, including returning to school in the autumn, thunderstorms in early summer and the winter respiratory virus season. Attacks during these periods are particularly inflammation driven and may therefore be readily preventable with regular or as required ICS[184] or biologics[240]. 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.
4. We must communicate the meaning and consequences of an asthma attack more effectively to our patients and to other stakeholders. The assessment of risk of a recurrent lung attack should be as big a part of the routine management of airway disease as it is in cardiac disease.

We could do more to understand the heterogeneity of asthma attacks at all ages, and the basis of 'wheeze attacks' in pre-school children. We have assumed that viral infection is the inevitable trigger, but bacteria are frequently isolated[154] (although whether cause or consequence is not easy to determine), and we need to understand if there are subgroups who should be treated with antibiotics without corticosteroids. Studies in patients with COPD lung attacks show that patients presenting in a similar way can have strikingly different patterns of airway inflammation[269]. There is increasing evidence 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[270,271]. Importantly, inflammatory patterns of attacks are repeatable within adult patients and can be predicted from findings when stable[269]. The 'treatable traits' approach to the treatment of stable airways disease discussed in section 2 could therefore be just as applicable in patients presenting during an acute attack, and in planning the best approach to prevention of a recurrence.

One interesting question is whether specific biological treatments have a role in treatment and secondary prevention of attacks, at least in adults. The IL-5 receptor blocker Benralizumab has a rapid and very complete suppressive effect on blood eosinophil count[272] suggesting that it might have utility as an alternative to prednisolone treatment in patients with eosinophilic exacerbations. There is already evidence that treatment reduces the rate of relapse in patients presenting with an attack[273]. The administration of an injected, long-lasting anti-inflammatory agent might have particular advantages in a situation where 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-agonist consumption, a high short-acting beta agonist/ICS 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[260]. Such a review could result in a risk score, similar to cardiovascular risk assessment, and an individualised recommendation for reducing risk. Might such an approach reap the same sorts of benefits currently being enjoyed in cardiovascular medicine?

SECTION 6: GETTING SERIOUS ABOUT SEVERE DISEASE

Where are we now?

The national report on asthma deaths (NRAD) stated that 60% of asthma deaths were in patients with 'mild' asthma[78]. This is clearly a nonsense, and our definitions of severe asthma must be wrong, since it is difficult to think of a worse outcome than death! The conventional definition is of symptoms, poor lung function and/or exacerbations (used interchangeably) despite being prescribed high dose anti-inflammatory and bronchodilator therapy[274]. This subset of patients (about 20% of the total) is referred to as having 'difficult to treat' or 'difficult asthma'. In many cases, after detailed systematic evaluation, a co-existent problem is identified (see Table 5 and 6), either alone (misdiagnosis) or together with mild/moderate asthma ('asthma plus'), and when effectively managed, symptoms can be controlled[275]. However, currently although lip service is paid to optimising basic management, in practice often very little is done beyond asking the patient if they are taking treatment. The biggest elephant in the room is adherence, an important factor even in those referred to tertiary level severe asthma centres[276]. A readily available protocol-driven adherence assessment would minimise the risk of committing a patient to long-term expensive biological treatment when their disease is readily controllable with inhaled treatments; one way, modifying medication delivery devices, is discussed above.

Some patients within this wider difficult asthma group have 'severe asthma', which cannot be controlled with currently available treatments 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 ICS plus a second controller for the previous year or systemic corticosteroids ≥50% of the previous year) to either maintain asthma control or which fails to achieve control (box 6)[274]. Severe asthma represents a significant unmet medical need and is the subject of intense mechanistic and therapeutic study, which needs to be brought into the clinic. Novel therapeutics, targeting a particular severe asthma phenotype (severe eosinophilic asthma), have started arriving in the clinic and will substantially increase management options for this group. Precise clinical assessment, with a particular focus on ICS adherence, is critical 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, where there is substantial remaining ignorance and therapeutic need. Ultimately, in all the asthmas, we need pathway defined approaches and treatments.

Where do we want to go?

A better definition

Difficult asthma is NOT a diagnosis but is an 'umbrella term' to describe a clinical problem, which requires careful multi-disciplinary assessment. It must be modified to include a component of risk, based not merely on airway phenotype, but also extrapulmonary co-morbidities and social/environmental factors. The first and most important challenge is to find a definition that includes risk assessment and reflects clinical reality. The recent ERS/ATS taskforce document definition[274] (box 6) recognised that different criteria can be used to define severe asthma and does not assume that these are pathogenically similar. Our proposals develop this important conceptual shift and focuses more explicitly on the risk of attacks:

- (all ages) one severe asthma attack should be taken as evidence of severe disease, and trigger a detailed evaluation of the disease
- Spirometry persistently below the normal range despite moderate doses of ICS and one other controller
- Persistent variable airflow obstruction despite prescription of a LABA and ICS combination
- (at least in adults) evidence of persistent airway eosinophilia despite the prescription of a moderate dose of ICS; however, symptoms per se, without evidence of airway eosinophilia, airway dysfunction and no history of exacerbations, should not qualify as 'severe' disease.
- Adverse factors in the behavioural/environmental domain: unscheduled visits, failure to attend appointments, poor adherence, smoking, allergenic environment and the three 'D's – Denial, Depression, Disorganisation.

Clearly a definition on its own achieves nothing; what this definition should achieve is a detailed and focussed response, assessing all aspects of the patient's airway disease, and the treatment plan, rather than assuming that an asthma attack is a mere minor inconvenience. Another need is a detailed and agreed assessment plan. After such an assessment, it may be clear that with good basic management the disease is no longer severe and risk has greatly reduced. However, short-term amendment may be followed by prolonged recidivism, and ongoing efforts to support better management are essential.

Tackling poor treatment adherence

The challenge of non-adherence to maintenance treatment exists in all chronic diseases and is also prevalent in difficult asthma. Here again, we have been slow to embrace modern technologies to assess adherence. Obtaining an electronic prescription record is easy but is not always done; if no prescriptions are being collected, then no medication is being taken. The next step, used in some

centres, is the use of a micro-chip to monitor when the device is being activated[277]. But this does not say that the patient is actually inhaling the drug correctly. It is not difficult to say that we need a device which 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 (say) three doses are omitted or rolling cumulative adherence drops below 80%, or, in the case of SABA, more than a set number of doses are taken in a particular time frame. We should mandate that all inhaled medications must be dispensed in such a device and so should healthcare payers. Naïve? We would ask why during our current technological revolution, inhaler monitoring technology has stalled, or rather, never got started in the routine clinic (see section 2).

Recent 'biomarker based' assessments of corticosteroid response may identify patients who should achieve good asthma control with better adherence to standard treatment and without escalation to some of the novel expensive parenteral biologic therapies[278]. Assessments of this kind must replace a 'suck it and see' approach to this needy 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

A number of comorbidities are commonly reported in a population with severe asthma (Tables 5,6) and management guidelines advocate identification and management of these conditions. However, the evidence that managing these comorbidities has a major clinical impact on asthma outcome in this population is limited. For example, despite a substantial literature discussing the relationship 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[279]. This may be because non-acid reflux is still occurring or because the presence of gastro-oesophageal reflux has little impact on underlying asthma but triggers cough perceived as asthma, either because asthma causes reflux, β_2-agonists increases reflux, or reflux is a harmless fellow-traveller. Gastro-oesophageal reflux can be effectively surgically treated with fundoplication and efficacy has been suggested in asthma[280]. However, a "sham controlled" fundoplication study has never been performed although this type of study is feasible and has been useful in assessing established surgical practice in other disease areas.

Similarly with obesity, the precise link with severe asthma remains unclear; however, discrete obese phenotypes have emerged consistently in cluster analyses of severe asthma cohorts[23,281]. 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[115]. However, the benefits of weight-loss reduction programmes and bariatric surgery, whilst encouraging, remain unclear[282,283]. As can be seen from these examples, a challenge for the future will be to tease out association from "cause and effect" for all of the commonly reported morbidities in severe asthma, which will allow better targeting of interventions, including invasive surgical procedures, in this patient group.

Precision, biomarker directed medicine in severe asthma

Recent data in adult patients with severe asthma, suggests there is evidence of more significant heterogeneity of airway inflammation. 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[10,23]. In severe asthma patients with no evidence of type-2 inflammation, it is likely that their corticosteroid dose has been escalated inappropriately to try and manage persistent symptoms which are not corticosteroid responsive[10]. Given the evidence that corticosteroid responsiveness is confined to type-2 high disease[6,284], 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. Adjusting corticosteroid treatment using sputum eosinophil count has demonstrated benefit in terms of exacerbation reduction at least in adults[10,11], but repeated sputum analysis has been challenging to deliver in routine clinical care, and the results are variable in children[285]. Moving away from the currently advocated symptom driven escalation of corticosteroid treatment, particularly in patients with severe asthma, will be a major component of delivering 'precision treatment' in severe asthma in the future and facilitate optimisation of corticosteroid dose. It would also allow a diagnosis of severe asthma to be made without escalation of corticosteroid treatment past a point where in many cases, there is unlikely to be any therapeutic benefit.

Some patients with type-2 high disease have refractory eosinophilic asthma, where despite adherence with high dose inhaled corticosteroids, there is persistent type-2 cytokine driven inflammation and airway eosinophilia. Currently, these patients (comprising around 3% of the total asthma population) frequently require regular or frequent courses of systemic corticosteroids to improve disease control. They develop well-recognised side-effects including osteoporosis, diabetes,

hypertension, cataracts, psychological disturbance, Cushingoid features, and airway and systemic infections[286,287]. 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 for some time. Clinical trials have demonstrated reduced unscheduled emergency visits and hospital admissions[288], and current guidelines advocate the use of Omalizumab as an add-on therapy in severe asthma[274]. However, it is problematic that serum IgE is not a useful biomarker of treatment response[289] and that there remains a reliance on non-specific clinical measures of asthma severity to guide prescription decisions[289]. The risks and benefits of biologics must be assessed objectively by biomarkers that are demonstrably and plausibly linked to the targeted biological process (i.e. FeNO for Omalizumab[289]). Otherwise, there will be an unacceptable and inefficient reliance on treatment trials in individual patients.

New biologic therapies targeting IL-5 are now available for use and other biological agents targeting type 2-high disease will potentially be available in the next 5 years (table 2). This will generate many interesting questions, including differential efficacy between monoclonal antibodies targeting IL-5 (Mepolizumab and Reslizumab), the IL-5 receptor (Benralizumab), IL-13 (Lebrikizumab, Tralokinumab) and IL-4Rα (Dupilumab). Other strategies inhibiting the type-2 axis including orally active CRTH2 antagonists (Fevipiprant)[290] and anti-TSLP[291] will also be targeting overlapping patient groups. Identifying which patients respond better to different classes of drugs may require 'head-to-head' studies, which are unlikely to be funded by Pharma. Many of these new therapies will come to market with a companion diagnostic or predictive biomarker of clinical response. Before release, it is essential that clinical trial data are made 'open access' and individual patient biomarker data analysed independently with the aim of identifying biomarker signatures predictive of efficacy of treatment. Patient organisations and healthcare payers should lobby pharma to ensure this happens.

There is already evidence that different biomarkers identify different aspects of type-2 mediated inflammation (tables 1 & 3). Both an elevated blood eosinophilia or FeNO is associated with the risk of severe asthma attacks but a greater risk is evident if both are elevated [100]. Existing data shows differences in the ability of biomarkers to predict treatment responsiveness. FeNO and serum periostin are good biomarkers of treatment response to biological agents inhibiting IL-13 in adults with severe asthma[29] whereas the blood eosinophil count is most closely associated with a response

to anti-IL-5[12] (table 3). Moreover, treatment with anti-IL-5 reduces the blood eosinophil count but not FeNO[12] whereas the reverse is true for anti-IL-13[29]. It is therefore possible that biomarkers profiles can be used to identify sub-groups of patients within the type-2 high population who have different risks of attacks and are particularly suited to different cytokine blockade. Whether post-hoc analysis of existing research databases is sufficient to tease such out these relationships is uncertain. Prospective information will be important and we suggest that biologics should: (a) only be prescribed in tertiary centres after a protocol driven assessment of why the patient is not responding to standard therapy; (b) should be subjected to a protocol driven therapeutic trial, with collection of clinical and preferably biological data in a standardised manner; (c) this information is collated and made available via a publically available database; and (d) more information is needed on treatment of severe childhood asthma.

All biological agents targeting type-2 cytokines have a larger impact on the risk of future attacks than on ongoing symptoms and lung function impairment (table 3). They are also likely to be expensive so health care payers will be keen for treatment efficacy decisions to be made early. This presents challenges as short-term changes in symptoms 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. It is also possible that this approach is not valid 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 based on 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 radio frequency energy to the airways with the aim of reducing airway smooth muscle mass and hyperresponsiveness. The role of thermoplasty in the management of severe asthma remains to be established. What is missing from existing clinical trial data is good evidence that response is linked to a particular pathophysiological abnormality, or trait (table 4)[292,293]. Thermoplasty treatment is thought to reduce airway responsiveness via a direct inhibitory effect on airway smooth muscle responsiveness, but such an effect has not been demonstrated 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[294], 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.

It is already clear that asthma symptoms and altered physiology often manifest in the absence of type-2 inflammation but we have limited information on what 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[139]. In addition, recent research has highlighted the association between systemic inflammation, especially systemic IL-6 inflammation and outcomes of severe asthma and raised the possibility that inflammatory mechanisms that arise outside the lung may cause lung injury[115]. These mechanism may relate to the inflammation that occurs with ageing and increasing body weight. Such mechanisms include inflammation associated with metabolic dysfunction including IL-6 pathways and pathways related to insulin resistance[115]. Importantly, some of these pathways are tractable in terms of treatment.

The greatest future challenge in severe asthma remains 'disease modifying' therapy and cure. It is attractive to speculate that if we could understand why patients with a pattern of disease (type-2 high), which is usually responsive to low doses of inhaled corticosteroids, becomes 'relatively' corticosteroid resistant and requires high dose (often systemic) treatment, we could target this therapeutically. This area has been the subject of study for many years, but no precise mechanism, as evidenced by a proven therapeutic, has as yet emerged.

SECTION 7. IMPROVING RESEARCH

Clinical trials

Over recent decades, clinical research has been characterised by randomised controlled trials (RCT) of moderate and severe asthma, in populations poorly generalizable to asthma patients in clinical practice[166], without characterisation of phenotypic subgroups, and inadequate consideration of other treatable traits related to overlapping disorders, comorbidities and lifestyle or environmental factors. It could also be argued that progress has 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 of 'me too' trials of ICS/LABA medications. The focus on moderate and severe asthma in trials based primarily in tertiary hospital

research institutions, has meant that there is a limited evidence base 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 the greater utilisation of primary care based research centres. However, the onus will then be on the primary care centres to improve diagnosis and monitoring of airway disease in their patients, and (not just in primary care) ensure that patients actually have an airway disease the nature of which is known, and are taking conventional medications appropriately before 'something new' is trialled. There is huge untapped potential for asthma research in primary care, which utilises electronic medical records containing clinical, laboratory and health utilisation outcome data. It is encouraging that this opportunity is being exploited so effectively in the Salford Lung Study[295] and by the Research Effectiveness Group[296].

Research also needs to encompass the spectrum of ages in which asthma occurs, including pre-school and school age children, in whom there is a paucity of clinical trials, yet paradoxically high burden of disease. For similar reasons, resourcing also needs to be provided to ensure more RCTS are undertaken in low and middle-income countries, as well as high income countries, and that medications are affordably priced for LMICs. The European Asthma Research and Innovation partnership have recently published an excellent report[297] emphasising the need for a joined up approach to future research in asthma and highlighting areas of particular need. This work provides a solid framework for improving the quality of research and, ultimately, asthma outcomes.

The issue of the external validity of evidence from RCTs is crucial in determining whether the findings inform the likely benefits and risks of a proposed treatment to individual patients. The traditional requirements of major RCTs to mandate that participants have marked bronchodilator reversibility, limited smoking histories, and designated symptom, reliever use or lung function parameters has 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 RCTs which have informed guidelines, on which recommendations for their management have been made[166]. Of course this may in part be because the asthma label is incorrect. The requirement for bronchodilator reversibility for participation in clinical trials has meant that the benefits of long-acting bronchodilators may have been over-estimated. Our failure to require evidence of active eosinophilic airway inflammation means that the benefits of ICS and other more specific inhibitors of this process may have been diluted and thus underestimated.

The Commissioners believe that features such as bronchodilator responsiveness, severity of asthma, diagnostic label, level of control, health care utilisation and smoking history should not be inclusion/exclusion criteria, but rather key covariates and potential predictors of response with the study powered for sub-group analysis. These would supplement the use of biomarkers of type-2 disease, which already have established utility as predictors of response to ICS and monoclonal antibody therapy directed against associated cytokines. In this way the findings from RCTs will not only be more generalizable to patients with asthma managed in clinical practice, but will also enable identification of sub-groups having a preferential beneficial, or a higher risk of adverse responses. Initial RCTs of broad populations could be followed by RCTs undertaken in highly characterised groups whose response to intervention is different in a clinically important way. Focused RCTs would also be applicable early on when the treatment target and its relationship to disease expression are well known. This approach will ensure that the findings have high external validity to such specific phenotypic groups. It would help rather than hinder the development of the precision approach to management outlined in sections 1 and 2. Table 4 provides information on the target population, potential covariates and most rational outcome measures for established treatable traits.

There is a growing awareness that while standard outcome variables such as lung function, composite measures of asthma control and health care utilisation provide a multidimensional assessment of efficacy and risk, they may be inadequate alone if a comprehensive assessment of efficacy and safety is to be obtained. This is illustrated in the differing, and at times heated, debate over the interpretation of the large RCTs of the single ICS/LABA maintenance and reliever therapy regimen, in which the lack of objective measures of medication usage contributed to the difficulty in assessing key outcomes such as beta agonist overuse, delay in seeking medical help during asthma attacks and systemic corticosteroid exposure[298]. A highly rigorous, RCT in high risk asthma subsequently showed the potential of electronic monitoring of medication use to objectively measure such clinical features of a therapeutic regimen[246]. This study not only demonstrated the favourable efficacy and safety profile of this single ICS/LABA maintenance and reliever therapy regimen in high risk asthma, but also set a new benchmark for RCTs in which patterns of medication use are electronically recorded.

There is also growing awareness of the need to place a greater emphasis on the investigation of the treatment of overlapping disorders, comorbidities, 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 may not only improve outcomes, but also move the field towards precision medicine in asthma.

Integrating epidemiology, genetics and translational research

A huge number of observational, cross-sectional and longitudinal studies have been performed lacking detailed clinical descriptions of affected patients; the basic science has been spectacular, the clinical characterisation limited. One of the main challenges to understanding the epidemiology and genetics of asthma is the lack of consensus in defining the disease, which is in part a consequence of the underlying heterogeneity (see section 1). Unless epidemiologic and genetic studies find better ways to distinguish between different diseases under the umbrella diagnosis of 'asthma' at a population level, it will be impossible to discover their unique underlying genetic risk factors, or identify novel therapeutic targets for stratified treatment, as any signal will be diluted by phenotypic heterogeneity[299]. This heterogeneity may result in discrepancies between different studies estimating asthma prevalence and associated risk factors. As an example, a recent review has demonstrated that in 122 epidemiological publications investigating risk factors for childhood asthma, no fewer than 60 different definitions of "asthma" were used[300]. However, it is of note that applying 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 participant may move from being considered "asthma cases" to "non-asthmatic controls", purely depending on which definition was used[300]. The overall impact 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 characterized subjects affected by wheeze, cough and asthma as in clinical settings by measuring in detail the traits we discuss in section 1 and in table 4. Fear of and malaise in cross-disciplinary collaborations between epidemiologists, clinicians, geneticists, immunologists and numerous other specialties has built up borders and fences and encapsulated visions.

Given the functional interdependencies between the molecular components in a human cell, mechanical characteristics of the lung, asthma is rarely a consequence of an abnormality in a single gene, a single environmental factor nor a single functional abnormality of the lung. Asthma reflects more 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 mechanism of a particular disease, leading to the

identification of disease modules and pathways, but also the molecular relationships among apparently distinct endo- or phenotypes[301].

While the complexity of the scientific world is ever increasing and specialties are struggling to keep up with the exponential rise of information and data, we have neglected to reflect about overarching general concepts of disease inception. Epidemiological attempts to isolate a few determinants out of a sea of confounding factors do not live up to a complex asthma syndrome, as discussed in section 3. We will not identify the magic bullet that will solve the asthma epidemic across the world. There is also very little appreciation that different biological pathways flow in clinical features termed 'asthma' which are not necessarily reproducible in other environmental and ethnic contexts. Striking examples are found in genetic studies where different genes for asthma are found in different ethnic groups[302].

Genetic research has addressed the hereditary component of asthma (usually defined as parentally or patient-reported "doctor-diagnosed asthma") in a number of large genome wide association studies (GWAS). While heritability estimates suggest that about half of the risk variation is attributable to genetic factors[303], GWAS have identified only a few common variants accounting for only a small part of asthma risk[304]. 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 GWAS accounted for only 38% of childhood onset asthma cases[304]. In addition to the GWAS initiatives, a wide array of candidate genes, all with weak effects, have been identified[305]. Of note, when a much more precise and specific definition was used (early-life onset asthma with recurrent, severe exacerbations in pre-school age), GWAS has identified associations with a much greater effect size, and novel susceptibility genes such as *CDHR3* (cadherin-related family member 3, rs6967330, $C_{529}Y$]).[306] Subsequent studies have shown that CDHR3 expression facilitates rhinovirus-C binding and replication, and that a genetic variant which was linked with hospitalizations for early-onset childhood asthma in birth cohort studies mediates enhanced RV-C binding and replication[307], providing further indirect evidence that we need to move away from using problematic umbrella terms in epidemiology and genetic studies. This sort of triangulated approach will be really important in future genetic and epidemiological studies.

Similarly, most of the known environmental risk factors for asthma also have weak effects[308], as discussed above. 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 relationships remains unclear. One of the most replicated examples of gene-environment interactions to date is that between endotoxin exposure and variants in *CD14* gene. Several studies have confirmed that high endotoxin exposure is protective against allergic sensitization, but only among individuals with a specific genotype (C allele homozygotes of *CD14/-159,* rs2569190), and not in those with other genetic variants[309,310]. A further complexity is added by the interactions with other environmental exposures (e.g. dust mite exposure), resulting in a complex gene by environment interactions[309]. Further examples include the observation that the same environmental exposure may have opposite effect on asthma among individuals with different genetic predisposition (for example, the effect of early-life day care attendance on asthma development goes in the opposite direction in children with different variants in the *TLR2* gene, with day care being protective in some, but increasing the risk in others)[311]. The lessons for intervention studies (including primary prevention) is that when identifying environmental protective/susceptibility factors which are amenable to intervention, individual genetic predisposition will have to be taken into account to enable the development of personalized strategies[312]. Thus, not only the treatment, but also prevention will have to be stratified.

Another often neglected issue is that the effects which are often attributed to environmental exposures may actually be a reflection of genetic predisposition (gene-environment correlation). Recent examples include the finding that the association between antibiotic use and childhood asthma (which is often attributed to antibiotics changing the host microbiome), may arise as a result of confounding, in which impaired antiviral immunity/increased susceptibility to virus infections increases the likelihood of both early-life antibiotic prescription and later asthma, with both asthma and early-life antibiotic prescription being associated with the same genetic variants on 17q21[313].

The translation 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 requirement for interventions to be easily introduced and taken up at the community level would enhance both participation in the research and its subsequent implementation if proven effective. This requirement is illustrated by the dilemma of the studies of multifaceted allergen avoidance/dietary/tobacco smoke avoidance strategies[314], 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 from high zone tolerance to the sensitization range. This concern, together with the expensive and burdensome nature of the interventions has limited 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 SABA for episodes of wheezing in infancy and whether it may increase the risk of established asthma in childhood. This hypothesis is based on the demonstration that inhaled SABA therapy increases airway hyperresponsiveness in both children and adults[315,316] and can do so within weeks. However, there would be major practical barriers encountered with attempts to undertake such a study, or change practice as a result of such a study, as any restriction in beta agonist use contradicts current dogma in terms of the treatment of wheeze in infancy.

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

We may require an innovative combination of trial design and statistical methods to overcome the main limitations associated with conventional RCTs. Such an innovative approach would be a randomised platform trial which uses Bayesian statistical methods, a priori 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[317]. Relevant subgroups could be identified, a priori, 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 may identify a beneficial effect early in the course of the disease would be an advantage. While 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 RCT. It also enables the study of additional novel interventions which are identified during the course of the study, which is important when the likely 10+ year duration of such studies is considered.

Animal models/basic immunology

Although we have made progress it has been incremental rather than paradigm shifting and we still lack adequate models in key areas. Current animal models do not adequately reflect the distinct clinical phenotypes and endotypes of human disease described above. Currently, the vast majority of models use mice and focus on Th2 phenotypes with high eosinophilia and a type-2 cytokine profile. There are no models that clinically cross-validate models of non-type-2 phenotypes. For example, there are no models that represent neutrophilic asthma, or those that adequately reflect steroid resistant phenotypes. The biology of neutrophilia is, however, very well understood- particularly in pulmonary infection models but translational studies are limited. Models of other clinically important phenotypes are also poorly addressed. There is almost exclusive emphasis on the acute phase of the host response to aeroallergens, and although there needs to be more focus on how to promote resolution of injury very few chronic exposure models exist. Genetic models of chronicity need to be cross-validated against human endotypes.

There is an excessive focus on the mouse as an experimental species, even though pathology in mouse and humans varies considerably[318]. "Mouse asthma" in most models is a disease of the peripheral lung as opposed to conducting airways. In addition, there is a failure to address genetic diversity issues - almost all 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 due to 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, as well as during different states of development. With the advent of CRISPR/Cas9 technology genome engineering has progressed to the point where it is possible to edit genes to reflect even subtle mutations and investigation into the function effects of SNPs identified in patient populations can take place. In contrast, genetic technologies have not been advanced in rat models, e.g Brown Norway Rats, which have previously been used to model allergic inflammation in vivo. Primate models, e.g., Ascaris sensitivity in Cynomolgus or rhesus monkeys are prohibitively resource intensive and ethically unacceptable in some countries; but should they be used more as a step between rodent and human studies? Sheep and horse models of asthma have also been described but their widespread use is limited by lack of resources as well as reagents for analysis. Excellent

data exists on comparative mouse lung functional physiology but it is not widely understood, thus impeding progress on understanding the functional basis of episodic airflow limitation.

We lack models that adequately address the interaction between viral (and bacterial and fungal) infections in asthma pathogenesis. This incorporates exacerbation models but in particular the clinical reality, which is concomitant challenge with virus/allergen. Generally, those that try and address the issue of exacerbation models focus on viruses[319]. There are beginnings of "relevant" respiratory infection models for mouse, including human rhinovirus (HRV), which is overwhelmingly the most applicable to humans, but the mouse HRV model is not really a good fit for human[320]. Most importantly, we have nothing yet to model the HRV-C subtype, which is the main pathogen in man in relation to asthma. Additionally, it is becoming increasingly evident that particularly during the initiation phase of asthma pathogenesis, bacterial pathogens play a central role as independent risk factors[321], and likely also via interaction with viral pathogens, but there is a dearth of relevant experimental models to probe underlying mechanisms.

Generally, the community is still focusing exclusively on specific pathogen free (SPF) mice, a fact that fails to take into account the microbiome perspective. This is completely at odds with the human situation in which the full spectrum of "hygiene hypothesis" related phenomena are relevant. For example, we know that Treg function is completely different between SPF and microbiologically "conventional" mice[322]. Moreover, microbial status during infancy determines maturation kinetics of both innate/adaptive immune functions and influences subsequent development of allergic responses[323].

There is a large-scale emphasis on immunologically competent adult animals whereas the main human caseload is in early paediatrics – a vital difference, considering that the immune system matures postnatally. We know from human epidemiology that fundamental changes occur in lung and airway growth pre- and postnatally as a result of immunoinflammatory episodes in the respiratory tract during pregnancy and infancy (see above). This obviously helps to set "trajectory" of lung/airway growth/differentiation, which influences development of lung function, but very few studies address this issue.

Translational biology (i.e. mouse and human "omics", GWAS, expression profiling) has not been systematically exploited. Technology to "humanise" mouse models is seldom utilized. The mouse is

extremely well understood for drug kinetic analysis but this knowledge is seldom 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 aetiology and pathogenesis. Specific examples include:

- why is it that only ~25% of sensitised/exposed children show clinically significant airways symptoms whereas 100% of sensitised/challenged mice respond?
- why is it that >90% of hospitalisations amongst school children for severe asthma exacerbations are in the midst of an acute virus infection, and of these >80% (probably more) are sensitised to indoor allergens ?
- why are most asthmatics under age 10 years boys? Yet most of the ongoing animal work is performed using female mice.

We need to establish an integrated platform whereby animal models form part of a framework that include 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[324]. We should not be afraid to embrace human in vivo models to answer particular questions that might shed light on molecular mechanisms underlying disease pathways[325,326].

RECOMMENDATIONS

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

1. Evolve from 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[327], to use asthma solely as a descriptive label for a constellation of symptoms (i.e. more akin to arthritis than CF). 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 at all. 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' (better, 'airway disease') this 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 its component parts before planning treatment, and also focussing in

particular on components that are treatable and are reassessed periodically for further treatment adjustment[118]. This general approach is equally applicable in patients with COPD and removes entirely the need to consider overlap categories such as ACOS.

We have identified traits that have the merits of being measureable, modifiable and linked to morbidity. We acknowledge that this is the start of the process and that better more well-defined traits may 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 where the two dominant identifiable and treatable traits (risk of attacks related to eosinophilic airway inflammation and symptoms as a result of airflow limitation) are assessed and managed, resulting in a more individualised and precision approach. This precision medicine approach is supplemented by broad consideration of treatable traits encompassing overlapping disorders, comorbidities, lifestyle and environmental factors. The simplicity of the approach, and the fact that it could be operationalised across different healthcare systems, makes it an attractive alternative to current guidelines. It has the additional merit of identifying the important gaps requiring 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[163] but this will need to be tested formally in appropriate healthcare settings. Assessment and treatment costs and measures of treatment efficacy are therefore logical outcome measures to use to assess the efficacy of this new approach and, since the use of ICS (particularly at high doses) will be impacted most obviously by the management approach, we suggest that an achievable goal would be to reduce high dose ICS consumption by 30% with no overall loss of symptom control and better control of attacks (see below).

2. Move beyond a disease control-based ambition for asthma treatment. We do not need more 'me-too' steroids and LABAs. Resources should be directed toward asthma prevention and cure. We want disease modifying studies, e.g. immunotherapy, early use of monoclonals, which involves finding biomarkers for risk in children, and a better understanding of initiation pathways for airway disease. And we want to provide older patients with hope that their chronic asthma may be cured.

Some encouraging initial progress has been made in this area[250]. Our goal is for at least one primary prevention strategy for high risk children and one disease modifying intervention to be identified.

3. Break out of our age- and discipline-related silos and see airway disease in the context of the developmental track from birth to old age. Regulators should be asked to enforce existing guidelines for mandatory testing plans for children as part of licensing process for new asthma drugs. And exploration of the benefits of intervening in utero to prevent asthma can be done, as the recent fish oil studies[250] and *Bordetella pertussis* vaccine studies have shown [328].

Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network may still be difficult to predict. For future research it is important that the correct principles and concepts are used. A reductionist approach is needed to identify involved mechanism and treatable traits, whereas systems biology need to be implemented in order to address the complexity of the interaction between different components and aging. Our goal is that the reductionist and system based approach are used as complementary, and that the right method is used for the right question.

4. *Test before treat*: We cannot implement precision diagnosis and management or make progress with prevention in children without moving away from the current 'no test' culture 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[329].

If, as discussed above, about a 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 old, early detection of this high risk group is relevant. First, to reinforce smoking cessation advice in parents and children[330], to implement regular follow-up of lung function and to start treatment as early as possible if needed in order to avoid or delay disease progression. Second, because if lung development has been suboptimal, it is conceivable that other organs might have also suffered similar developmental abnormalities[235]. If this was the case, the early identification of low lung function by spirometry in early adulthood may have public health consequences that reach well beyond respiratory diseases. Spirometry is cheap and straightforward and there are probably several good opportunities 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. Aligning testing to a highly

focused and effective educational campaign on the dangers of smoking might have a bigger impact 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 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 affect this change. We hope that changing the name may startle us out of thinking in the rut and change our limp response to these sentinel events to something nearer the cardiologists' focussed, highly effective and life changing response to a 'Heart attack'. We should look again at our current 'one size fits all' approach to treatment and secondary prevention of attacks. Might a more precision approach offer more? Is there a role for biological agents? We will push research in these important areas across the spectrum of acute wheezing illnesses as the impact on health care systems and patient outcomes could be large.

In terms of prevention, we anticipate that measuring biomarkers will help identify at risk patients and perhaps help them make a decision to commit to life-long prophylactic treatment. We see value in the development of a risk score[260], which could be incorporated into an annual review, and might help to move us from secondary prevention to primary prevention of attacks. The Commissioners will drive the development and validation of this. We have considered difficulties related to 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. Consideration will need to be given to replacing as required SABA with ICS/fast-acting β_2-agonists as reliever therapy in patients with episodic symptoms, depending on the results of ongoing RCT's. This regimen has the potential to have a big impact on the occurrence of severe unexpected attacks[9]. Overall, we see this area as one where very significant progress is possible and consider a realistic goal to be to reduce attack frequency hospitalisation, 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 impact as heterogeneity of clinical and biological aspects is more obvious in

severe airways disease[23]. The biological era of treatments will start at about the same time as this commission in published. We must be sure that we use these agents effectively in individual carefully characterised patients. Basic aspects of management must be mastered before going down this path. 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 in having simple and reliable biomarkers of response to biological treatments in school-aged children and adults and potentially in pre-schoolers[329]. We will need to move from a traditional disease category/symptom/lung function based assessment of treatment need and response to one where decisions are driven by the presence and responsiveness of the relevant trait. We must make progress in the 'which biological for which patient' sphere by collating phase 2 and 3 clinical trial data and carefully collected post-registration patient data with the goal of identifying responsive sub-groups. Trial data must be made available for individual patient data analysis. This is another area where very significant progress is possible. A realistic and very important goal from the patients' perspective is to reduce by 50% exposure to regular and rescue oral corticosteroids.

7. Better research. The commissioners will work in collaboration with Pharma to ensure that future clinical trials establish not only treatment efficacy and safety but identify definable sub-groups 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 measure to those associated with 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 lunacy of trialling bronchodilators in patients selected on the basis of the presence or absence of a bronchodilator response at baseline, and evaluating drugs targeting eosinophilic airway inflammation in patients who don't have this characteristic.

We suspect that these changes will be readily understood and accepted by regulatory authorities such as the FDA as their primary concern is that trials are carried out in well-defined populations. Currently this means populations that have the diagnostic characteristics of the condition (i.e.

'asthma' or 'COPD') set out by relevant guidelines. When the guidelines change, so will the authorities. However, we must ensure that they are aligned to any proposed change. Our goal is for clinical trials of the future to focus of 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 'test before you treat', we insist on 'test before you research' – what airway disease is actually being studied? Our goal is to 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[331]. Animal models need to be closer to real life, including pregnancy exposures, viruses and allergens, rather than just single factors. Despite the cost of large animal models, these represent an important stage between mice and men. Using a range of animal models offer us the best prospect for unpicking the complex interplay between different inflammatory pathways, defining why aberrant inflammatory pathways perpetuate and identifying preventive strategies.

The time traveller from the days of Harry Morrow-Brown and the earliest use of cellular markers to guide treatment[2] would find that, while technology and molecular biology have progressed hugely, in airway disease very little has changed at all. What will a time traveller from today find in 25 years' time? It is the hope of the Commissioners that this will be objective, biomarker driven analysis of airway diseases across the age spectrum, rather than facile umbrellas; 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 on the basis of real-time data transmitted to patients and physicians, with consultations using modern communication methods; and those at high risk in the up and coming generation (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 to spin out into research, whereby the geographical diversity of airway diseases is appreciated not ignored; that the sophistication of scientific studies will be matched by appropriate clinical assessment of the disease; and that animal models will truly reflect human disease. This Commission represents a chance to start this process; and if it is ignored, the time traveller from the 1950's will still find us stuck in the rut in the 2050's.

CONTRIBUTORS

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

CONFLICTS OF INTEREST

IDP reports grants from GSK, Afferent and Atopix; honoraria and speaker fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GSK, Almirall, Dey Pharma, MSD, Schering-Plough, Novartis, Napp, Regeneron, Teva, Knopp, Chiesi and RespiVert. RB reports personal fees from Health Research Council of NZ, GlaxoSmithKline, AstraZeneca, Novartis and grants from AstraZeneca, Chiesi, Cephalon, Genentech, GSK, Novartis, Sanofi Aventis. AA reports grants and personal fees from Astra-Zeneca, GSK, MSD, Menarini, Novartis and personal fees from TEVA and Chiesi. GPA serves on advisory boards for Novartis, GlaxoSmithKline, AstraZeneca, Pieris Pharmaceuticals and Boehringer Ingelheim. EB reports personal fees from Sanofi, Novartis, AZ, TEVA, GSK, Vectura, Boehringer, and grants for research from GSK, AstraZeneca, Roche, Novartis. GB has received fees for lectures and advisory boards from Astra Zeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva and Zambon. PC has nothing to disclose. AC reports personal fees from Novartis, Regeneron / Sanofi, ALK, Bayer, ThermoFisher, GlaxoSmithKline, Boehringer Ingelheim. FMD has nothing to disclose. JF reports grants from Pfizer, Genentech and Vitaeris; he is named inventor on a patent describing biomarkers of Th2 high asthma and on a patent describing thiol modified carbohydrate compounds as novel mucolytic drugs (no income). UF has nothing to declare. PG reports grants from NHMRC Australia and personal fees from AstraZeneca, GlaxoSmithKline, Novartis. LGH reports grant funding from MedImmune, Novartis UK, Hoffmann-La Roche/Genentech Inc., AstraZeneca and GlaxoSmithKline; has taken part in advisory boards and given lectures 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 (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim and GlaxoSmithKline); and has taken part in asthma clinical trials (GlaxoSmithKline, Schering-Plough, Synairgen and Hoffmann-La Roche/Genentech), for which his institution was remunerated. He is also Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with Amgen, Genentech/Hoffman-La Roche, AstraZeneca, Medimmune, Aerocrine and Vitalograph. PGH has nothing to disclose. MH reports personal fees from Astrazeneca, grants and personal fees from GSK, personal fees from Novartis, personal fees from Roche, Sanofi and TEVA. CL has nothing to disclose. GM reports grants from AstraZeneca, grants from GlaxoSmithKline, Novartis Pharmaceutical and the International Union

Against Tuberculosis and Lung Disease. FDM reports grants from NIH/NHLBI, NIH/NIEHS, NIH/NIAID, NIH/OFFICE OF THE DIRECTOR, and Johnson&Johnson, personal fees from Consultancy to Copeval and Commense. PDS has nothing to disclose. EvM reports personal fees from PharmaVentures, OM Pharma, Decision Resources, Novartis Pharma SAS, The Chinese University of Hongkong, University of Copenhagen, HAL Allergie GmbH, Ökosoziales Forum Oberösterreich, Mundipharma, American Thoracic Society, AbbVie Deutschland GmbH & Co. KG, University of Tampere, European Commission, Massachassuetts Medical Society and American Academy of Allergy, Asthma and Immunology. SW reports grants and personal fees from AstraZeneca, GSK, Boehringer-Ingelheim , Genentech, Sanofi-Regneron, and Novartis and personal fees from Knopp. HJZ has nothing to disclose. AB has nothing to disclose.

ACKNOWLEDGMENTS

No sponsorship was sort or received. We thank the Lancet for making their offices available for a Commissioners meeting in May 2016. Commissioners covered their own travel and accommodation expenses to attend this meeting.

Legends to Figures

Figure 1: Crude asthma mortality rates 1960-2012 for the 5-34 age range in 46 countries and the two main eras of asthma management. The locally weighted scatter plot smoother rates with 90% confidence intervals, weighted by country population, are shown in red. The association of the inflammation based era with improved outcomes can readily be observed, as can the flat-line with regard to further improvements since 2005.

Figure 2: Prevalence of symptoms of asthma in the last 12 months among people aged 18-40 around the globe (World Health Survey 2002-3)[84]**.**

Figure 3: Comparative effect sizes expressed as odds ratio for asthma exacerbation rates for the use of mepolizumab 250mg IV for asthma, when applied using control-based paradigm (Unselected), and when used in a targeted therapy paradigm in patients with severe eosinophilic asthma (Targeted)[109]. Significant benefit in an important subgroup is missed if all comers are treated

Figure 4: Different pathways leading to eosinophilic airway inflammation.

Figure 5: GINA 2014 asthma management guidelines

Figure 6: Ongoing monitoring of the two dominant components of airways disease and precision management. *Rapid onset beta-agonist/ICS combination is the default rescue medication

Figure 7: Patterns of airway disease through the ages with main traits. Gaps indicate no data

Figure 8: Hypothesis 1. The relative risk contribution to later asthma is composed of a multitude of small effects. The small effects originate from various subsystems or compartments (e.g. immune system, airway growth, epithelial function, etc.). Each compartment or subsystem has its own timing and phase of development. Their relative importance for asthma (arrows) may be age- dependent. Vulnerability (window of opportunity) to environmental stimuli will likely vary at different age periods in each compartment. The overall temporal evolution of health and disease will be affected by the complex temporal interplay of all these compartmental subsystems.

Figure 9: Hypothesis 2. Since not all compartments of the respiratory system mature at the same age, the relative contribution (expressed in circle diameter) of each compartment (C1 to C5) to the overall behaviour of the normal, but also abnormal, function of the respiratory system may change during development. E.g. the relative importance of small airway size will (exemplified by compartment C2) diminish with age for wheezing disorders, whereas other key compartments, e.g. the immune system in the sensitized child, will become dominant or even critical with increasing age (exemplified by compartment C5).

Figure 10: Hypothesis 3. Depending on how environmental stimuli affect or even alter the development of the various compartments, the phenotypical expression of the disease may be different as well as age-dependent. E.g. Savinjie et al[46] demonstrated that risk factors for transient or intermediate onset asthma are qualitatively similar, but quantitatively different than for persistent asthma. Illustrated in this model, the relative contribution to the overall disease risk of small airway size (C2) and sensitization to any allergen (C5), respectively is quantitatively different in

transient wheeze (phenotype 1) than for persistent wheeze (phenotype 3). Very likely, in a large population of asthmatics, there will be overlaps between distinct asthma phenotypes.

Biomarker	Association with treatment response	Invasiveness	Comments
FeNO	Corticosteroids, anti-IL-13, anti-IL-4&13, anti-IgE	Non-invasive	Easy, quick, not specific, cheap, generally available. Loses specificity in smokers[332]
Serum IgE	Not associated	minimal	Although recommended to measure, there is no clear association between IgE or allergy as a biomarker of treatment responses or clinical outcome[289]
Serum Periostin	Anti-IL-13, anti-IgE	minimal	Effect shown with Anti-IL-13, limited availability currently. Confounded by growth in childhood, pregnancy and dental disease[333]
Blood eosinophil count	Anti-IL-5, anti-IL4/13 (?)	minimal	Generally available, high clinical impact, predicts anti-IL-5 response and ICS response in COPD[101]. Associated with increased risk of lung attacks[100,101]
Sputum eosinophil count	Corticosteroids, Anti-Il-5, anti-IL4/13 (?)	moderate	Specialist centres, tissue specific, time-consuming. Good therapeutic marker for ICS, OCS, biologics. Established evidence of value as a monitoring tool.

Table 1. Potential biomarkers of eosinophilic airway inflammation. FeNo= fraction of exhaled nitric oxide; IgE = immunologulin E

Area	Drugs (number)	Market entry profitability			Cumulative
		PHASE II	PHASE III	Approved	
HIV/AIDS	108	75	50	39	14
Dermatology	122	8	44	29	11
Haematology	163	60	4	22	9
Neurology	192	73	47	22	8
Cancer	68	78	46	20	7
Cardiovascular	280	69	4	22	6
Respiratory	165	68	31	16	3

Table 2. New drug discovery in different fields of medicine[19]. Figures represent percentage unless otherwise indicated.

Monoclonal antibody	Biomarker used for patient selection	FEV[1]	AHR	ACQ	Exacer-bations	OCS - sparing effect	QLQ	Blood eos.	Sputum eos.	FeNO	Serum IgE	Comments
		Effect on clinical endpoints						Effect on biomarkers				
Anti-IL-5	Blood and sputum eos. count, exacerbation rate.	+	0	+	++	++	++	↓↓	↓	0	0	Clinical effects in specific subgroup of severe asthma
Anti-IgE	Blood IgE, spec. IgE level and positive SPT*, FeNO*, blood eos.*	+	0	+	++	unclear	+	↓	↓	↓↓	0	Most RCT's focused on moderate to severe asthma, less evidence in very severe asthma
Anti-IL-13	Periostin level, FeNO	+	unclear	+	+	N/A	0	↑	unclear	↓↓	↓	Partially based on subgroup analysis
Anti-IL-4/IL-13	Periostin, FeNO and blood eos., ,	+	unclear	unclear	++	unclear	N/A	↑	unclear	↓↓	↓↓	Promising agent potentially offering more efficacy than achieved with single cytokine blockade[334]

Table 3. Effect of Type 2 associated monoclonal antibodies on clinical markers and biomarkers in severe eosinophilic asthma. *Not yet used for patient selection but shown to be highly predictive of a response.

+ = clinically improved; 0 = measured and no effect observed; N/A = not attributable/not measured; unclear = measured, not enough data points for conclusion. Exp, expected; FEV1, Forced Expiratory Volume in 1sec.; AHR, airway hyperresponsiveness; ACQ, asthma control questionnaire; OCS, oral corticosteroid; ICS, Inhaled corticosteroid; QLQ, quality of life questionnaire; eos., eosinophils; FeNO, fraction of exhaled nitric oxide; IgE, Immunoglobulin E; RCT, randomised controlled trial; IL, Interleukin.

		Recognition	Treatments	Likely impact of treatment	Factors associated with better treatment response	Comments
Variable	ASM contraction	$FEV_1/FVC < LLN$ Bronchodilator reversibility and short-term PEF variability consistent with variable airflow obstruction and large component of ASM contraction ICS/OCS response consistent with inflammation related airflow limitation (i.e. mucosal oedema, mucus plugging) Loss of airway support probable if imaging or physiological evidence of emphysema	$Beta_2$-agonists (SABA and LABA) Antimuscarinic agents (i.e. LAMA) Theophylline Bronchial thermoplasty? Loss of airway support may respond to lung volume reduction strategies	**Patient related:** Symptom scores QOL Small reduction in attacks (particularly less severe) Exercise capacity **Surrogate:** FEV_1 PEF Airway responsiveness	Acute bronchodilator response Airway hyperresponsiveness Eosinophilic airway inflammation	Different classes of bronchodilators have additive effects Bronchodilator therapy increases probability of patients discontinuing ICS. 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. 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.
	Mucosal oedema					
Airflow limitation	Mucus plugging					
	Loss of airway support					
Fixed	Small airway fibrosis					
Eosinophilic airway inflammation		See table 1	ICS and OCS See table 3	**Patient related:** See table 3 **Surrogate:** See table 3	See table 1&3	Different biomarkers provide complimentary information[100] Suspect episodic inflammation in patients with

					episodic symptoms Some 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 (i.e. long-term low dose macrolides) Inhaled interferon-β (viral infection) Influenza vaccination Antifungal drugs (?only effective in those sensitised to aspergillus and colonised)	**Patient related:** Reduced attacks Symptom scores QOL **Surrogate:** Small improvement in FEV_1 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/OCS Stop ACE inhibititor	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Cough senstivity	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 middle aged females Sometimes due to factors in table 5

Table 4. Pulmonary treatable traits of airway diseases

Component	Recognition	Treatments	Likely impact of intervention	Factors associated with better treatment response	Comments
Rhinitis/gastrooesophageal reflux/	Suggestive symptoms Imaging Oesophageal manometry	Nasal steroids PPI	**Patient related:** Symptom scores QOL **Surrogate:** Improved imaging appearances Nasal inspiratory flow Oesophageal manometry	Chronic rhinitosinusitis with polyps can be difficult to control with nasal steroids	Causes of asthma-like symptoms but direct link with lower airway disease unlikely
Obesity/deconditionoing	BMI Cardiorespiratory exercise test	Weight loss Bariatric surgery Rehabilitation/exercise training	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Reduced BMI Improved 6 minute walk test	Absence of co-morbidity Good social support Group participation	Bariatric sugery most effective intervention for obesity Link with lower airway disease poorly understood
Anxiety/dysfunctional breathing/vocal cord dysfunction	Disproportionate breathlessness, air hunger Frequent sighs Dizziness, light headed, tingling hands and face Chest tightness Inreased Nijmegen questionnaire score Noisy inspiration	Physiotherapy Rebreathing Anxiolytics Counselling Speech therapy	**Patient related:** Symptom scores QOL	Early recognition	Important but poorly understood causes of morbidity

Depression	Hospital anxiety and depression scale	Antidepressants	**Patient related** Symptom scores	May be associated with increased risk of death	Particularly important in severe disease
Treatment associated morbidity	ACE-inhibitor associated cough Breathlessness/tiredness secondary to β-blocker	Withdraw or replace treatment	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Reduced cough sensitivity Improved 6 minute walk test	ACE-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 and/or risk factors Restrictive spirometry Abnormal CXR and/or CT	Of the underlying condition	Specific to underlying condition	Treatable condition	Cardiac disease commonly coexists and can be difficult to tease apart relative contributions

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

Component	Recognition	Treatments	Likely impact of intervention	Factors associated with better treatment response	Comments
Smoking and other environmental exposures	History Urinary cotinine Exhaled CO	Cessation Treatment for nicotine addiction (NRT, Varenicline)	**Patient related:** Symptom scores QOL Reduction in attacks Exercise capacity Increased survival **Surrogate:** FEV_1 PEF Neutrophilic airway inflammation Reduced decline in lung function	Smoking history Addiction potential (?genetic) Presence of pre-existing lung disease	Difficult to modify Treatments for nicotine addiction doubles chances of sustained quitting Impact 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 (i.e. latency) Relevant exposures Skin prick tests/RAST tests	Avoidance Desensitisation ICS and OCS Omalizumab ? Air filtration systems	**Patient related:** Symptom scores QOL Reduction in attacks Remission **Surrogate:** FEV_1 PEF Airway responsiveness Eosinophilic airway inflammation	Good evidence of sensitisation Monosensitisation Early recognition	Limited evidence base Timing of intervention may be critical May be epiphenomenon
Treatment adherence and device related factors	Prescription refill rates Drug levels FeNO supression test Chipped inhalers	Counselling and education Better inhalers Maintenance and reliever therapy with ICS/SABA or ICS/LABA (MART) Mobile/IT reminder technology	**Patient related:** Reduced attacks Symptom scores QOL Reduction in attacks **Surrogate:** Improvement in FEV_1 Reduced sputum eosinophils and FeNO	Poor inhaler technique more tractable than adherence issues	Common but difficult to detect and modify

Social and behavioural issues	Social history Home visit School/workplace information	Support	**Patient related:** Symptom scores QOL		Difficult to modify, particularly in adults

Table 6. Important environmental and behavioural factors potential associated with asthma-like symptoms

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After asthma – redefining airways diseases. A *Lancet* commission

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'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' Kola and Bell[1]

Executive summary

Asthma is responsible for significant global morbidity and health care costs. Significant progress was made against key outcomes such as hospitalisation and asthma mortality in the 1990's and early 2000's but there has been little improvement over the last 10 years despite escalating treatment costs. New assessment techniques are not being adopted and progress in new drug discovery has been slower than in other specialities.

~~The commission asked experts in a large number of fields, linked by a common expertise in asthma, to consider why this might be. We discussed where thinking and management should be in the 21st century, and how best to get there. An important early goal was to move out of age (paediatric, adult), discipline (basic science, epidemiology, clinical research), disease and nationality related silos and attempt to think in a joined up way. Our list of commissioners, all acknowledged experts in their respective fields, were chosen to reflects this goal. We met in person on three occasions between November 2014 and September 2015 and participated in numerous teleconferences. Each Commissioner identified ten areas where they felt progress was most pressing. These 'points for progress' were organised into seven themes and working groups were assembled to discuss each (box 1). 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.~~

~~By far the most commonly identified theme was the need for a basic rethink of the way we classify and think about all aspects of asthma and other airway diseases. The quote at the start of this section, from a recent review discussing poor progress in new drug discovery, is particularly pertinent. It is now clear that our outdated physiology based classification system for airway disease provides a very limited perspective on the heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in our patients. Our over simplistic concept of disease, and assumption that all asthmas are the same, nearly resulted in us missing the significant clinical benefits of Corticosteroids[2], which remain the most important treatment class available to us, and Mepolizumab, a monoclonal antibody targeting the type 2 cytokine interleukin (IL) 5[3] now known to be highly effective in severe eosinophilic asthma. Simplistic concepts of disease are, we~~

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~~believe, the most important cause of a stalling in improvements in key clinical outcomes in the last 10 years despite ever increasing spending on asthma treatment[4].~~

In this document we set out to provide ~~a summary~~our view of where we are and where we need to go as a community of clinicians and researchers who tackle the significant public health problem that is asthma. The document should be seen not as a comprehensive review but more of an opinion article, reflecting the collective view of the Commissioners (referred to hereafter as we). It is also a call for action to all clinicians involved in the~~a~~ field ~~where there has been a slowing of progress against key outcomes and a reluctance to adopt new technology and thinking~~. The aim of the C~~c~~ommission was to identify entrenched positions where progress has stalled and to challenge dogma, and the results have been integrated into seven sections.

In the first section of the document we argue that our physiology-based classification system for airway disease is outdated as it provides a very limited perspective on the heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in our patients. The quote at the start of this section, from a recent review discussing poor progress in new drug discovery, is particularly pertinent. It is now clear ~~that our outdated physiology based classification system for airway disease provides a very limited perspective on the heterogeneous mix of pathobiologically distinct mechanisms responsible for morbidity and mortality in our patients. O~~that our over simplistic concept of disease, and assumption that all asthmas are the same, nearly resulted in us missing the significant clinical benefits of Corticosteroids[2]~~, which remain the most important treatment class available to us,~~ and Mepolizumab, a monoclonal antibody targeting the type 2 cytokine interleukin (IL)-5[3]. T~~; t~~hese entrenched concepts ~~y~~ ~~now known to be highly effective in severe eosinophilic asthma. Simplistic concepts of disease~~ are, we believe, the most important causes of a stalling in improvements in key clinical outcomes in the last 10 years despite ever increasing spending on asthma treatment[4].

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We suggest~~argue~~ that the only way we can make progress in the future is to be much more clear about ~~the~~ meaning of the labels we use ~~and~~ acknowledge the assumptions that go with them. ~~We suggest that a~~Airway diseases ~~are~~ should be deconstructed into ~~components~~ traits that can be measured and, in some cases, modified (treatable traits), and which are set in the context of social/environmental factors and extra-pulmonary co-morbidities. An important catalyst for this change has been the discovery of simple and clinically accessible measures of one of the most influential and treatable ~~component~~traits~~ of airway diseases~~:

eosinophilic airway inflammation[5]. 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[6] and ~~. T~~the use of these biomarkers to stratify patients has been instrumental in recent successful new drug development[7,8].

The second section considers how this new approach could be operationalised in all healthcare 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 (ICS) ~~to be~~are used in a more targeted, biomarker directed and hopefully efficient way. The Commissioners considered at length the risk that moving from a 'more ICS in more lungs' to a 'more ICS in the right lungs' approach might jeopardise the large improvements in key outcomes seen between 1990 and 2005 with the former approach. An important missing bit of information is the long-term safety of withholding ICS in patients with low biomarkers of eosinophilic (or type-2) inflammation. Our pragmatic solution is to use an as required combination low-dose ICS~~/ in combination with~~ rapid onset β_2-~~agonists~~ agonist inhaler ~~in~~ as the default reliever option so that ~~all~~ patients with episodic symptoms and airway inflammation are more likely to receive ICS at a critical time, while acknowledging that this approach needs to be tested. We suggest ~~but to not escalate~~ that ICS treatment is not escalated beyond this unless biomarkers of type-2 inflammation are increased. There is a substantial rationale for this approach and support from clinical trials[9]. Once established on treatment we need to improve monitoring from 'how are you?' 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 for our views on the development and evolution of airway diseases through infancy, childhood and adult life. Much more needs to be done to allow this proposed deconstruction of airway disease in non-invasive ways across the age spectrum. Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network may still be difficult to predict, in part because these mechanisms are superimposed on a system that is developing in childhood and declining during senescence. In order to make sense of this additional complexity it is important that the correct principles and concepts are used. Dominantly, a reductionist approach is used to identify involved mechanism and treatable components, which can lead to novel drug developments or therapeutic concepts. On the other hand, if we want 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 in order 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, but also that we need to move on from current birth cohorts, informative though these have been, if we are to address the fundamental causes of asthma, and move beyond satisfaction with the status quo and toward an ambition to prevent or cure asthma.

When thinking about asthma treatment we tend to focus on established asthma, rather than the fundamental underlying causes. This has set the agenda for asthma as a chronic disease that we should try to control rather than one we should try to conquer. The fourth section asks whether we can modify the inexorable progression from intermittent early childhood wheeze to persistent asthma in the teen years followed by a life sentence of therapeutic drug dependence. We call for no more 'me too medicines' but a commitment to develop treatment approaches that focus on prevention and cure.

The next two sections discuss two areas where 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 ~~a given~~the patient, and we propose a re-thinking of current 'one size fits all' approaches to treatment and secondary prevention of attacks. ~~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[10,11] or with highly selective biologics inhibiting type-2 inflammation[12]. The use of as-required ICS/~~ combined with~~ rapid onset β_2-agonists as the default reliever option is likely to provide an effective solution for the small number of patients with episodic, but ~~high risk~~high-risk disease who figure 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 ~~asthma~~ will align well with an approach that is of acknowledged value in severe asthma[6,7,13]; however, we must use the tools of modern molecular and systems biology to tease out even better biomarkers of risk and treatment response. Their use will be essential for us to make the most of the increasing numbers of new treatments that selectively inhibit type-2 inflammation.

We finish with a section calling 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 ~~characteristic~~ trait we are seeking to modify or study rather than arbitrary diagnostic labels (particularly those lacking any precision, such as 'Dr-diagnosed asthma'), and we should choose an outcome measure related to this ~~characteristic~~ trait and relevant to patients. Using models because they are there (systemic sensitization of mature mice, for example) 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 FDA, reviewers of manuscripts and grant funding agencies are rightly concerned that trials are carried out in well-defined populations but must this mean that they have the diagnostic characteristics of an arbitrary condition (i.e. asthma or COPD) set out by current guidelines? We think not, but we must ensure that all of these stakeholders are aligned to any proposed change.

Perhaps ambitiously, we propose a revolution in thinking about asthma, generalizable to all airway diseases, which, alongside the undoubted importance of optimal delivery of the best care to each patient, will deliver real precision asthma medicines, dissecting airways disease into its components 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 shake us out of a rut, diverting us away from a diagnostic and therapeutic *cul de sac* and result in a new system that will be valuable in epidemiological and interventional studies and make it more likely that we unpick pathophysiology and, eventually, develop better medicines and achieve better outcomes for our patients. We hope it will add momentum to the recent encouraging progress in new drug discovery and, as did the first asthma guidelines 27 years ago, lead to a decade or more of improved outcomes. We finish by formulating seven key recommendations and summarising our views on how these could be developed to the benefit of our patients (box 1).

~~In summary, we have for too long ignored the complexities of airway disease by hiding behind umbrella terms and by propagating unproven (and in many cases unlikely) assumptions. Our hope is that this Commission will shake us out of a rut, and result in real progress over the next decade. We finish by formulating seven key recommendations and summarising our views on how these could be developed to the benefit of our patients (box 1).~~

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"Wherefore is this* disease different *from* all other diseases?" *Maurice Pappworth

INTRODUCTION

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It is 275 years since the first asthma guidelines were written[14-17], and "asthma" was identified as a disease associated with airway inflammation. This led to the much more widespread use of inhaled corticosteroids (ICS) instead of repeated and even regular doses of short acting β_2-agonists (SABA) as primary treatment, with great benefit to many patients (figure 1). However, progress has slowed over the last 10 years despite increased spending on treatments[18] and we have not seen the developments in new drug discovery enjoyed by other specialties[19]. Our central position is that the most important cause of this stagnation is a continued ~~and complacent~~ reliance on outdated and unhelpful disease labels, treatment and research paradigms and monitoring strategies, which have reached the stage of unchallenged veneration and have stifled clear thinking.

Imagine a rheumatologist diagnosing 'arthritis' or a haematologist 'anaemia' and generically treating without determining the specific type and cause in the 21st century. The notion is ludicrous. Yet, the umbrella term 'asthma' continues to be applied to the disparate group of conditions characterised by varying degrees of airflow obstruction (both fixed and labile); different (or no) patterns of inflammation; contributions from bacterial and viral infections which vary over time; an over sensitive cough reflex; and mucus hypersecretion. Despite a proliferation of research papers studying the pathology of asthma and identifying fundamentally different patterns of disease, especially airway inflammation, we are still stuck with this stereotypic label, and asthma therapy has really not progressed much over the last 20 years; it is still 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[20]. This simplistic chain of reasoning has become that wheeze or cough equals asthma equals eosinophilic airway inflammation equals need for prescription of ICS. If by chance the symptoms have the temerity to persist, this means that eosinophilic inflammation is refractory and more treatment must be given.

Concern about outdated disease taxonomy was expressed by our forefathers in 1958[21] and again in a Lancet comment in 2006[22], but little has changed. A catalyst for change has been the development and clinical use of non-invasive methods to assess airway inflammation[5]. These techniques have shown that 'asthma' and other airway diseases consist of a heterogeneous mix of pathologically distinct processes poorly represented by our current physiological and symptom-based classification system[6,7,23] and have opened the door to a new precision medicine type approach to management. Eosinophilic airway inflammation has emerged as particularly important as it is readily recognisable

and is associated with the risk of attacks that can be prevented with corticosteroid treatment[6]. 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[10,11,24,25], and the same basic approach works well irrespective of the diagnostic label. Moreover, it has been shown convincingly that biological agents that specifically inhibit eosinophilic airway inflammation by blocking the type-2 cytokines interleukin (IL)-5, IL-13 and IL-4 have important beneficial effects when given to adult patients with airways disease and this pathology, but not when evaluated in all comers with 'asthma'[3,12,26-29]. It is now clear that a new form of stratification of airway disease will be essential if we are to make the most of the opportunities provided by these new biological treatments. The *absence* of eosinophilic airway inflammation is also important – it means that ICS should not be escalated, with all the attendant risks of side-effects, and new treatment possibilities should be considered.

Our concern is that continued reliance on an approach that over-simplifies and over-generalises a complex and heterogeneous syndrome ('asthma') will result in us missing other pathogenically important and tractable mechanisms. New thinking is needed and we hope that this Lancet Ccommission will stimulate this. Theis Ccommission is predicated on the assumption that 'asthma' is no more a 21st century diagnosis than 'arthritis'[30], and will attempt to liberate this mix of airway diseases from the protective but limiting diagnostic label 'asthma' to reflect the clinical and pathologic heterogeneity of different "asthmas" and allow the management of these diseases to progress to the next level.

The aim of this commission The commission asked experts in a large number of fields, linked by a common expertise in asthma, to consider why this might be. We discussed where thinking and management should be in the 21st century, and how best to get there. An important early goal was to move out of age (paediatric, adult), discipline (basic science, epidemiology, clinicaland clinical research), disease and nationality related silos and attempt to think in a joined up way. Our list of Commissioners, all acknowledged experts in their respective fields, were chosen to reflects this goal. The Commissioners met in person on three occasions between November 2014 and September 2015 and participated in numerous teleconferences. Each Commissioner identified ten areas where they felt progress was most pressing. These 'points for progress' were organised into seven themes and working groups were assembled to discuss each (box 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 positions where progress

has stalled and to challenge dogma. ~~The results have been integrated into seven themes chosen after each commissioner identified their own ten most important 'points for progress'.~~ Each theme addressed the same questions:

1. Where are we ~~stuck~~ now~~, and why is it such a bad place~~?
2. Where do we think we ~~need~~ want to go?

This Commission would be a sterile process if we did not set ourselves goals and we finish by identifying seven key recommendations (box 1), along with our ideas for operationalising them and assessing their impact.

SECTION 1: CHANGING THE WAY WE THINK ABOUT AIRWAYS DISEASE

Developments in thinking on 'Asthma' over the years

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Asthma has been recognised since antiquity. The word comes from the Greek ασθμα, meaning a 'short-drawn breath, hard breathing, or death rattle' (box ~~2~~3) 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; there was also recognition of an association with environmental factors, including climate and geographical areas. Sir John Floyer[31], who suffered from asthma, provided the first modern treatise on the disease in 1698 (box ~~2~~3), and identified bronchial constriction as a cause for wheezing. He was also the first to describe asthma attacks and potential triggers by providing a first-hand account of his own experiences. Salter[32], himself also an asthmatic, provided a more formal definition of asthma in the late 19th century (box ~~2~~3) and recognised that asthma *' …. if it is at all severe and its attacks frequent , cannot long exist without inflicting permanent injury to the lungs..'*. This 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 impact of this condition (box ~~3~~4).

Francis Rackemann, a distinguished Boston physician, carried out 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[33]. 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.' 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 intrinsic to the body associated with older age at onset and the absence of atopy[33].

The association of asthma with variable airflow obstruction was formally recognised soon after spirometry was introduced by Hutchinson in the 1840s and the association with a low forced expiratory volume in one second/vital capacity (FEV_1/VC) ratio was described by Tiffeneau in the 1940's[34]. Bronchodilator reversibility has emerged as the diagnostic test of choice although the validity of this test has never been properly addressed[35] nor has it been recognised that this test tells us nothing about the presence and nature of underlying airway inflammation. Bronchodilator treatments, including epinephrine, anticholinergics, methylxanthines, and inhaled β-agonists were all introduced in the first half of the twentieth century and, early in the second half, systemic corticosteroids were identified as a potentially useful treatment. The introduction of systemic corticosteroid treatment in the 1950's in the UK was not entirely straightforward as an early and influential MRC sponsored clinical trial showed little useful efficacy and highlighted a high potential for systemic toxicity[36]. Harry Morrow-Brown, a young chest physician working in Derby, England was surprised by these negative findings and went on to use his medical student microscope to show that there was clear efficacy in patients with asthma who had eosinophils present in their sputum smear but not in those without[2]. He used a similar method of patient selection to show in the early 1970's that inhaled B~~b~~eclomethasone D~~d~~ipropionate was an effective topical treatment when administered by aerosol and that treatment mitigated the adverse effects of oral corticosteroids by allowing a significant number of patients to withdraw this treatment without loss of asthma control[37,38]. This work was widely ignored over the next 50 years but in retrospect was pioneering and important as 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 been long appreciated in paediatrics, and a large number of studies can only briefly be summarised here. In the 1960's, both Selander[39] and Fry[40] in different contexts astutely observed that episodes of infant wheeze were temporally associated with outbreaks of viral infection in the community, but these infant wheezers did not develop asthma in childhood. Jeremy Cogswell, a general paediatrician in Poole, took the matter further in a small but stellar study showing that early exposure to house dust mite was of great importance to the

development of early childhood asthma, but was irrelevant to wheeze in infancy[41,42]. More long-term studies have confirmed that there are a number of different patterns of wheeze. The Melbourne cohort, which has reached the sixth decade with around 75% retention, has shown that lung function tracked throughout the study period, with those who just wheezed with viral colds ('wheezy bronchitis' as it was initially described) having normal lung function throughout the life course, but children with asthma, and particularly severe asthma, having permanent obstructive defects. Indeed, the children with severe asthma had a more than 30-fold increased risk of 'chronic obstructive pulmonary disease (COPD)', and this group had the worst lung function at age 10 years[43]. The clinical differences between those who wheeze with viral colds and 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[44].

Perhaps the classical cohort study was from Tucson, which followed babies from birth and initially reported on wheeze at two time points, age three and six years[45]. The timing of study visits meant that only four wheeze phenotypes could be discerned: never wheeze, transient early (0-3 years only), persistent (0-6 years) and late onset (3-6 years), with different characteristics and evolution over time of lung function. Mathematical modelling in big cohorts with more data points or information from healthcare records (ALSPAC, PIAMA, KOALA, Dunedin, Manchester, Rotterdam)[46-52] have discerned more phenotypes concluding that subtypes of childhood wheezing can be identified based on the temporal pattern on wheezing. However, there were important differences 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[53]. These studies have ~~established~~ identified numerous potential risk factors for asthma onset, including maternal asthma[54] and smoking in pregnancy[55], mode of delivery[56], low birth weight[57], impaired lung function[58,59] and airway hyperresponsiveness shortly after birth[60-62], and the importance of early microbiological exposures[63]. Also, just as it has long been appreciated that all wheeze is not equal, it is becoming clear that there are different patterns of atopy, with differing significance[50,64-67]. Hence the combination of sensitisation to multiple allergens and persistent wheeze with acute attacks is most predictive of a long term adverse outcome[51,66,67]. Finally, the differences between the factors *initiating* atopic asthma, and those propagating the asthmatic condition, have become appreciated. Three excellent randomised controlled trials of the early initiation of ICS in infants at risk for the development of asthma have relieved symptoms but shown no effect of this treatment on the natural history and progression of wheezing[68-70], and the limited studies of the pathology of infant

wheeze have shown no eosinophilic inflammation in most[71], whereas of course properly administered ICS are excellent suppressive treatment for recurrent or persistent asthma with eosinophilic airway inflammation.

Over the last 50 years it is possible to identify two main eras of asthma management each lasting about 25 years: the bronchodilator era, starting with the introduction of increasingly selective inhaled β_2-agonists in the mid-1960's and focusing on airway hyperresponsiveness as the key pathophysiological abnormality; and the anti-inflammatory era, starting in the late 1980's, where more aggressive use of ICS was emphasised and airway inflammation was seen to be of central importance (figure 1). It should be noted that, despite clear evidence of lack of correlation between inflammation and airway responsiveness, and the differential response of each to different treatments[72] the myth that airway inflammation was the origin of all asthma troubles was sedulously cultivated. This 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 hospitalisation rates with 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 β-agonist or high dose poorly selective β_2-agonist inhalers[73-75] (figure 1). Underuse of ICS has also contributed to asthma deaths (and depressingly still does)[76]. This association, and the increasing recognition that airway inflammation was commonly seen even in patients with mild asthma[77], fuelled the second era. However, over-reliance on inhaled β_2-agonists still contributes to asthma deaths[78].

Increased use of ICS proved to be a more difficult sell than the use of β_2-agonists, in part because treatment had a less rapid and therefore less obvious ~~immediate~~ ~~short term~~ impact on symptoms. Guidelines were used to encourage patients and prescribers to introduce ICS earlier and patient education with multidisciplinary input was employed to encourage continued adherence with treatment once a symptom response had occurred. This second era was associated with an impressive reduction in hospitalisation rates and mortality from acute asthma, particularly over the ensuing 10-15 years in children (figure 1). Corticosteroids do not totally obliterate acute bronchodilator reversibility; one third of patients in the Brompton severe asthma registry still have reversible airflow obstruction despite a depot injection of triamcinolone[79]. It became clear that combinations of inhaled long-acting β_2-agonists (LABA) and ICS resulted in superior outcomes for many[80,81]. However, worryingly, at least in children and despite the complete absence of any evidence, there is an increasing trend to prescribe combination therapy as first line preventers. Still

more worryingly, it is possible to prescribe LABA as a single agent, despite compelling evidence that: (a) people use them without concomitant ICS; and (b) this increases the risk of asthma deaths[82].

It is of great concern that progress against key outcomes has stalled in the last 10 years and preventable deaths continue to occur with depressing regularity despite increased investment in treatment. This could be explained partly by variations in practice, as there are marked regional and international differences in these outcomes, related in part to access and affordability of asthma therapy as well as variations in asthma symptom prevalence[83,84] (figure 1 and 2). In Finland, for example, a well-coordinated and highly effective national campaign focusing on asthma control resulted in a marked reduction in hospitalisations due to asthma[85]. However, although the overall approach was found to be cost-effective, treatment related costs were significant, and the guideline and self-management approach that were the cornerstone of the Finnish approach have been more difficult to implement elsewhere. There is also a more fundamental concern that our current 'one size fits all' management approach cannot be safe and deliver better outcomes to everyone even despite greatly increasing treatment costs, unless our diagnostic and management paradigms are optimised.

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

Definition and basic concepts

The most widely used Global Initiative for Asthma (GINA) 2002 definition of the disease (box 2) is a lengthy description of pathological, physiological and clinical features that encompass the major disease characteristics (airway hyperresponsiveness, structural changes to the airways or airway remodelling, disordered mucosal immunity and chronic airway inflammation)[86]. The latest 2014 definition (box 2)[87] is less descriptive and moves away from these features but, nevertheless, they are still commonly highlighted as important.

Implicit in making abnormalities in airway physiology, airway structure, and airway immune function part of the definition of 'asthma' is that these abnormalities are well defined, homogeneous, universally present, causally linked and readily measureable. The reality is that they are none of these. Although we can measure abnormalities in airway physiology, we cannot easily measure abnormalities in airway structure, or airway immune function. ~~For example, p~~This is a problem as promising treatment approaches for the abnormal airway response to viral infection[88] may not succeed until we have new techniques to assess this component. Similarly, improving airflow

limitation is an important goal of management, but we will not be able to modify this until we can distinguish between the limitation that is due to an active, treatable factor and that which is irreversibly programmed in early life or prenatally.

Diagnostic and monitoring approach

Despite the protean manifestations of 'asthma' discussed above, our main approach to diagnosis has been to document asthma symptoms and variable airflow limitation, and this approach has changed little in 50 years. Reliance on measures of airflow obstruction is problematic for six reasons.

(i) ~~-~~Lack of consensus on how to demonstrate variable airflow limitation. Definitions of abnormality are not closely related to the normal range for that measure (i.e. bronchodilator reversibility). Moreover, the measurement characteristics of different tests are not well studied[89] 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 where the clinical question is whether a symptomatic patient has 'asthma' or an alternative explanation for their symptoms. Some tests (i.e. peak expiratory flow variability) have been shown to be grossly abnormal in patients with very pathogenically different conditions such as dysfunctional breathing or vocal cord dysfunction[89]. There is thus a large potential for misclassification.

(ii) Difficulty measuring lung function in primary care. Tests of variable airflow limitation are relatively difficult to do in non-specialist settings where most cases of asthma are diagnosed, but also in pre-school children in any clinical context. This is particularly the case for assessment of airway responsiveness. This is unfortunate as tests of airway responsiveness are sufficiently sensitive ~~so~~ that a negative result provides strong evidence against a diagnosis of asthma. A result of the relative difficulty of pulmonary function tests in in the primary care setting and the absence of rule out tests has been that primary care clinicians feel they have few options other than a 'trial of treatment' approach with ICS. This approach is flawed because the mimics of asthma (which often do not respond to corticosteroids) ~~have a tendency to improve spontaneously over time~~cause variable symptoms and may therefore improve spontaneously over time, leading to the mistaken belief that ICS treatment 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 (i.e. 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, together with the tendency of clinicians to be cautious in borderline cases, increase the likelihood that patients may be started on inappropriate ICS therapy, with associated cost and potential toxicity. There is increasing evidence that over treatment is common: observational studies showing that 60% of patients referred to secondary care[90] and 30% of patients in primary care[91] have no objective evidence of airway dysfunction or inflammation and do not deteriorate when ICS treatment is stepped down. One result ~~i~~ of inhalers being given away free with Cornflakes is that the diagnosis of asthma has become trivialised. This may be one of the reasons we struggle to sell the need for long-term treatment to an increasingly sceptical population.

(iii) Identifying at risk patients. Current diagnostic approaches for asthma do a poor job identifying patients who are at high risk for serious outcomes. This problem is evidenced by data from national enquiries into asthma deaths showing that patients with asthma perceived to be mild and low risk continue to die of the disease[78]. Strategies are needed that identify high risk disease more clearly, and engage patients in ways that encourages 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.

(iv) Disadvantages of umbrella diagnostic terms. Conventional wisdom is that asthma and COPD are distinct, and guidelines suggest very different management approaches[86,87,92], particularly in the way we use ICS. The reality is that there is very significant overlap, 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[93]. The clinical communities response to this overlap has been to invent another umbrella term: Asthma COPD Overlap Syndrome (ACOS)[94]. This acronym has the demerits of combining what we argue to be two problematic umbrella terms to make a third one that is even more problematic[95]. ACOS may be characterised by a COPD-like systemic inflammatory profile; ACOS, asthma and COPD may be neutrophilic, eosinophilic or mixed; and bronchodilator reversibility fails to distinguish anything from anything else[96]. 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 irrespective of the label[96,97]. Given that this is the case for many features of 'asthma' and 'COPD' then the importance of applying the label becomes questionable and it may even be counterproductive because of the clear potential for misclassification and inappropriate use of ICS and LABA monotherapy.

(v). Poor treatments for poorly characterized airway diseases. Failure to look beyond our current diagnostic labels limits exploration of causes of morbidity in patients who have chronic cough or wheezing associated with viral respiratory tract infections. These are airway diseases with a relatively distinct clinical phenotype but they are not easily placed in the current classification system for asthma or COPD. As a result, we have only a superficial understanding of the mechanisms of these common problems and no specific treatment approaches. Many patients sit uneasily under the 'asthma' umbrella and receive regular asthma treatment with little evidence of benefit. Our failure to clearly identify and study these specific patient populations means that there is almost no interest from industry, and thus few prospects for effective treatments.

(vi) *Equation of variable airflow obstruction with eosinophilic airway inflammation*. The identification of variable airflow obstruction in the definition and diagnostic process for asthma may be one reason why it is widely assumed that this pattern of airway dysfunction identifies a discrete airway pathology (eosinophilic airway inflammation). This is now known to be incorrect[26]. Severe eosinophilic airway inflammation may even be associated with loss of bronchodilator reversibility[98] and 40-50% of patients with objective evidence of variable airflow obstruction have non-eosinophilic pathology (or no detectable airway inflammation)[99]. Thus, whilst 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 disconnect between defining characteristics of 'asthma' and outcomes that really matter (risk of attacks, likelihood of a response to corticosteroid treatment) may be another reason why clinicians have tended to adopt a 'no-test' approach to diagnosis. However, we have seen rapid progress in the development of biomarkers of airway inflammation. For instance, we now have several reliable markers of eosinophilic airway inflammation, which provide a better perspective on risk of attacks[100,101] and the likely response to treatment with corticosteroids[6,101,102] than traditional physiological measures (table 1). Some of these biomarkers (i.e. 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[6]. There is increasing evidence that these biomarkers stratify risk effectively and results in more effective and economical use of currently available and new treatments[6,25,101]. The howls of rage from some quarters at the suggestion by the UK National Institute for Clinical Excellence (NICE) 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 instituted, without any objective diagnostic measurements ever being made. Is there any other chronic disease for which objective diagnostic tests are readily available of which this can be said? Although the Ccommissioners differed in their views on the strength of evidence for diagnosis and management guided by biomarkers, particularly in children, there was a consensus that the incorporation of biomarkers into the diagnosis could only enhance the capacity to diagnose asthma responsive to ICS and lead to a paradigm shift from the current approach to diagnose the umbrella term asthma, to the diagnosis of asthma phenotypes that respond to specific treatments.

New drug development

Until recently we have not seen the developments in new drug discovery enjoyed by other specialty areas (table 2)[19]. This area perhaps exposes the limitations of our current view of 'asthma' and airway disease most obviously. New asthma treatments are largely variants on the old; a browner inhaler, with more potent topical effects, despite increasing concerns about topical immunosuppression[103]. When new treatments become available, they are widely prescribed to all comers despite being largely ineffective (Sodium Cromoglycate, Ketotifen) or effective only in subgroups of patients (Omalizumab, Mepolizumab). There has been, until recently, no concept of targeted treatment. 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)[19].

Mepolizumab, a humanised monoclonal antibody that was developed to inhibit eosinophilic airway inflammation by blocking interleukin (IL)-5, is a good example. Mepolizumab was found to be safe and effective at blocking IL-5 and reducing eosinophilic airway inflammation when tested with *in vitro* systems and *in vivo* models[104,105]. A subsequent clinical trial was designed based around incorporating Mepolizumab into a step-up guideline-based paradigm[106]. Within this paradigm, Mepolizumab was investigated in patients who remained symptomatic on current ICS therapy and the clinical trial focused on lung function and asthma symptoms as traditional outcome measures. Despite adequate power, this trial was unexpectedly negative. This led to much soul-searching and the near-abandonment of the drug[107].

Investigators who were experienced with non-invasive measures of airway inflammation identified two important problems with this initial clinical trial: first, the heterogeneity of airway inflammation in severe asthma meant that a significant number of the trial participants would not have had eosinophilic airway inflammation and therefore would not be expected to respond; and second, the

occurrence of asthma attacks is closely linked with eosinophilic airway inflammation[13,26,107,108] and might have been a better outcome measure than lung function and asthma symptoms. Two investigator-initiated studies were designed targeting Mepolizumab specifically to patients with severe asthma and sputum eosinophilia and using asthma attacks as an outcome[26,108]. In both studies, Mepolizumab treatment was associated with decreased asthma attacks with effect sizes of 50% - 80% (Figure 3)[109]. Subsequent phase 2b[12] and 3[110,111] studies 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 obstruction and symptoms, previously regarded as essential defining characteristics of asthma, were of no value in predicting treatment response[12,98], nor seemingly was the label of asthma as robust treatment responses were seen in patients with features of COPD provided there was evidence of eosinophilic airway inflammation[12]. The same general principle has been instrumental in the development of a range of biological agents targeting IL-5[112,113], IL-13[28,29] and IL-4 & 13[27] pathways, many of which are showing encouraging signs of efficacy in late phase clinical trials (table 3).

Where do we ~~think we need~~ want to go?

The Commissioners believe that what is needed is a third era of asthma management, which takes into account the increasingly recognised heterogeneity of asthma and offers precision management based on a careful assessment of the characteristics of a patient's disease and targeted treatment. This will be particularly important if we are to take advantage of the bounty of drugs that inhibit type-2 inflammation. It is also necessary in order to identify other pathogenically important and tractable mechanisms.

One important question is whether the phenotypic heterogeneity of asthma can be explained by discrete mechanistic pathways, or endotypes[114]. For example, it is possible that the systemic inflammation associated with obesity and older age may have effects in the airways to worsen asthma[115]. This is a complex area as there is a limit to how much phenotypic heterogeneity can inform our understanding of endotypes because many phenotypic traits (i.e. symptoms, airflow obstruction) can be caused by multiple disease mechanisms[114,116], –just as many kidney diseases cause uraemia. For this reason, a reductionist approach, which focuses on traicomponents that are recognisable, linked to morbidity and associated with treatment response may represent a better conceptual framework to accelerate progress towards personalized treatments[116-119]. We can focus

short-term on these treatable traits while searching for mechanistic underpinning. The important principle is that mechanisms ultimately will drive the precision.

Treatable traits

Any biological tube reacts with a very limited and stereotypic set of responses, *irrespective of the underlying cause*. This is hardly a revolutionary concept: irrespective of how it is damaged, the failing kidney cannot excrete creatinine, and blood levels rise. Based on the thinking of the late, great Freddie Hargreave[120], and with the introduction of several new ~~components~~traits, the stereotypic responses of the airway to adverse events are (in rough order of importance and recognisability) any or all of:

Airflow limitation

This is a treatable trait if due to repeated contraction of airway smooth muscle and perhaps airway wall inflammatory oedema (mural); and/or intraluminal factors (airway secretions). However, variable airflow limitation may be due to less treatable problems such as loss of alveolar guy ropes (extramural). All that wheezes is not airway smooth muscle contraction, and the cause of wheeze and its response to treatment needs to be appreciated. Furthermore, paediatrics challenges the conventional view of airway hyperresponsiveness; just as there are multiple atopies (discussed below), there are multiple hyperresponsivenesses. Three prospective birth cohort studies have demonstrated that airway hyperresponsiveness is present within weeks of birth, at a time when there is no evidence of allergy, airway inflammation or increased airway smooth muscle mast cell infiltration[121], and is strongly predictive of medium term respiratory outcomes[60-62]. Animal and a limited amount of human data suggest the underlying cause is change in airway dimensions (elongation and narrowing) and loss of airway tethering points, such that any narrowing of theairway leads to an exaggerated obstructive signal[122]. Multiple subsequent additional and potentially more treatable factors are likely to contribute including sensitisation of airway nerves, mast cells and smooth muscle by inflammatory mediators[123]; reduced epithelial barrier function; reduced production of bronchoprotective factors[124]; an intrinsic abnormality of airway smooth muscle[125]; and some of the structural changes to the airway discussed below[123].

Airflow limitation may be unresponsive to bronchodilators and anti-inflammatory treatment. While this may not be a treatable trait, fixed airflow limitation is certainly one that can lead to overtreatment if not appreciated. Early life factors may be the most important causes of the airway structural changes leading to fixed airflow limitation[47,126-128]. The birth cohort studies show that

these first develop antenatally and in early childhood and studies in adults show that, although there is a subset of patients with rapid deterioration in spirometry, many people, with or without asthma or COPD, have normal lung aging[129]. Early lung function loss may be related to circumferential narrowing or elongation of the airway itself, which may be developmentally determined in utero[130], or postnatally, related to viral infection (obliterative bronchiolitis)[131,132] and pollution[133]; or loss of the alveolar tethering points (an important mechanism maintaining airway calibre is the alveolar 'guy rope' attachments; there are animal data that these are reduced by antenatal smoke exposure[134]). Airflow limitation has been demonstrated soon after birth, for example in the infants of mothers who smoked in pregnancy[135], long before there is any evidence of airway inflammation[71,136]. It can be worsened by antenatal or postnatal exposure to pollution[133], again likely independent of eosinophilic airway inflammation. The consequences of pre-term birth and early life bronchopulmonary dysplasia are another increasingly recognised cause of fixed airflow obstruction in later life[137].

The presence of a significant number of patients with asthma who have fixed airflow limitation provides a clear potential for clinically important misclassification if umbrella terms continue to be utilised. This problem disappears if we move towards a more precise and clinically useful approach that uses only the term "chronic airway disease" (like anaemia, see above) and, then, goes on to describe the particular treatable traits present in a particular individual. Definition of fixed obstruction may not be easy in an individual, and in children in particular there is no agreed definition of an adequate treatment trial for this purpose. Sometimes airflow obstruction is apparently fixed but responds well to anti-inflammatory treatment, presumably as a result of improvement in airway oedema and/or mucus plugging. However, the possibility that airflow ~~obstruction~~ limitation is fixed and due to poor lung development or irreversible structural changes should always be considered before escalating treatment ~~in the face of ongoing airflow limitation~~ when evidence of airway inflammation is lacking.

New imaging techniques and more sensitive physiological measures might provide new and clinically important information about mechanisms leading to fixed and variable obstruction, but until then the underlying causes of airflow limitation cannot be assumed to be always due to discrete treatable traits. We suggest that 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 may be necessary to do this.

Airway inflammation

Airway inflammation is heterogeneous among patients with a label of 'asthma'. Eosinophilic airway inflammation is an important pattern as 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 the master regulator lymphocyte population and probably also in their responsiveness to treatment with ICS (see figure 4)[138], and there may be others, hitherto undiscovered. The exact mechanisms and the clinical implications of involvement of these different pathways remain to be defined but they could theoretically represent individual distinct treatable traits. Given the proliferation of high cost monoclonals, we need to understand pathways in the individual patient rather than go forward with a haphazard series on N-of-1 therapeutic trials.

Prospects for identifying and modifying airway inflammation in Type 2 low disease are much more uncertain[139,140]. We have therefore not included this as an individual treatable trait. Some encouragement that it might be is provided by the beneficial effects of long-term low dose macrolides in patients with non-eosinophilic asthma[141,142] but CXCR2 antagonists, which cause a marked reduction in sputum neutrophil counts[143], have no efficacy in patients with uncontrolled asthma[144]. In patients with COPD macrolides and CXCR2 antagonists have very different effects in smokers and ex-smokers, with the latter effectively reducing exacerbations in smokers but not ex-smokers[145] and the former having the opposite effect[146]. These findings suggest that there are at least two types of neutrophilic airway inflammation in patients with airway disease, differing in their relationship with smoking and airway infection. Indeed, neutrophilic inflammation may be *beneficial*[147] in the presence of airway bacterial infection (which is increasingly implicated in asthma, below), as a recent cystic fibrosis (CF) trial of an anti-LTB_4 strategy demonstrated[148]. The important lesson of this trial was the mere presence of inflammation is not a sufficient reason for obliterating it.

Neutrophilic airway inflammation might also be driven by Th17 mediated processes. In a first clinical trial, Brodalumab, which blocks IL-17 signalling by inhibiting the IL-17 A receptor, did not improve Asthma Control Questionnaire (ACQ) scores (primary endpoint) in a group of moderate to severe asthmatics[149]. Treatment did have beneficial effects in a subgroup with high reversibility to salbutamol although this finding was not confirmed in a subsequent unpublished phase 3 trial. A selective beneficial effect in bronchodilator responsive patients with severe asthma has also been reported with the TNF-α antagonist Golimumab, although this treatment was not pursued as there

was a high incidence of malignancy in the treated population[150]. Patient selection was not optimal in either the Golimumab or Brodalumab study as the presence of neutrophilic airway inflammation was not confirmed and ~~there was no~~ markers of TNF-α[151] or IL-17 involvement were not included as criteria for patient ~~for~~ selection. It remains possible that there is a definable sub-group of patients with severe asthma who derive net benefit from one or both of these treatments.

Airway infection/impaired airway defences

There is little doubt that viral infections are an important trigger for acute severe asthma and growing evidence of an abnormal airway response to infecting respiratory viruses resulting in an amplified airway inflammatory response and worse clinical consequences[152,153]. Challengingly, bacterial as well as viral infection has been shown to be present in acute asthma attacks[154]. Both are potentially identifiable and are therefore candidate treatable traits in patients with 'asthma' and there is existing evidence of efficacy of inhaled interferon-β in patients with severe asthma[88]. However, before we rush to antibiotic therapy for attacks, it should be noted that an equally plausible reason for positive bacterial cultures is transient, viral-induced topical immunosuppression.

Altered cough reflex sensitivity and efficacy

Cough is clearly an important airway defence mechanism, and the best treatment is to remove the underlying cause. There are significant age-related changes 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 are receiving high intensity treatment with little or no evidence of benefit[155]; little is known about the extent to which this is a factor in children. Adult p~~P~~atients are usually middle aged females presenting with a persistent dry cough associated with a heightened cough reflex, often in the absence of other features of airway disease[155]. Only a small proportion of patients have cough reflex hypersensitivity secondary to treatable eosinophilic airway inflammation[156]. Other treatable causes include cough secondary to angiotensin converting enzyme inhibitor treatment; however, a significant proportion has no obvious cause[155]. This component of airway disease is recognisable and quantifiable[155]; it is an important area for new research and for new drug development and there are encouraging signs of progress[157]. Similarly, reduced sensitivity or effectiveness of the cough reflex, related for example to medication or neuromuscular disease respectively, could theoretically be treated with cough augmentation techniques.

Conclusions

We acknowledge that it may not be possible to determine all the facets of airway disease in every patient, especially children, but the potential complexities should at least be appreciated. Spirometry is difficult for young children to perform and it may not be sensitive enough to detect important abnormalities in some patients[158], but other reliable lung function techniques exist, which are less dependent on cooperation by toddlers and infants and may be more sensitive[159,160]. Lower airway inflammation can only be assessed in severe cases as bronchoscopy is not justified in most children with asthma. Measures in nasal secretions and breathomics 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. It is also clearly impractical to go through this mantra in patients with mild airway disease where there is little diagnostic doubt, for example in primary care in particular; the adult or child with an airway disease that is completely responsive to low dose ICS will clearly not want to submit to multiple airway tests! It is also clear that they are not separate discrete entities; for example, chronic airway bacterial infection may lead to neutrophilic inflammation and increased airway secretory products. It is obviously of particular importance to give heed to the currently treatable manifestations of airway disease whilst not losing sight of the need to develop novel therapies for currently intractable issues. Finally, we need to remember that some or all of these traits may have implications in the time domain as well as immediately, specifically conferring future risk even despite there being no apparent immediate harm. This has important implications, which we will discuss in a later section.

Precision management

"And Socrates said 'he who first gave names and gave them according to his conception of the things which they signified; if his conception was erroneous, shall we not be deceived by him?'"

Richard Asher taught that we still muddle up clinical observations and pathology, and name entities in a muddled way, leading to muddled thinking[161]. This is EXACTLY what has happened with the term 'asthma', where guidelines have conflated symptoms (cough, wheeze, and breathlessness), physiology (variable airflow obstruction) and pathology (eosinophilic airway inflammation). So we must describe what we see, using the framework in table 4 as at least a starting basis, acknowledge the gaps in what we know, and use terminology to illuminate not obscure. So asthma becomes a syndrome, and a diagnosis for a given individual should now become (say) 'an airway disease/asthma syndrome characterised by fixed and variable airflow obstruction but no eosinophilic airway inflammation or chronic infection' where high dose ICS will not ~~therefore~~ be prescribed and future risk will be quantified and modified where possible. In the future, perhaps we will be able to

say ‘an asthma syndrome characterised by mutations in the IL-X pathway leading to excessive neutrophil chemotaxis in response to pollutants, with secondary structural airway changes’ and prescribe an anti-IL-X monoclonal antibody if we cannot remove the underlying cause.

Until then we have the traits of the asthma syndrome discussed above and in table 4. These at least have the merits of being linked to morbidity, and some at least are reasonably well defined, measureable, associated with morbidity and linked to specific treatment responses. We recommend these traits are used to structure an alternative approach to assessment and management, along the lines recently suggested by Agusti and colleagues[118].

The first generic question when the physician assesses a patient of any age is whether there are comorbidities or lifestyle factors that might be contributing to the clinical problem? Identification and modification of these traits (see tables 5 & 6) is likely to be helpful irrespective of whether the patient has underlying airway disease. The second question is~~, which~~ what aspects of the patient’s problems are due to airway disease? Assessment of the clinical history, the presence of risk factors of airway diseases (smoking, allergies, occupation, family history, and respiratory disease in early life), spirometry, and readily accessible biomarkers of type-2 inflammation should go a long way to answering this key question. If there is considered to be a high probability of airway disease, the next step is to determine which traits are driving airway disease in this particular patient and treat them accordingly, being mindful of the likely outcomes of that treatment (table 4). If airways disease seems unlikely, or is refractory to simple treatments, or morbidity is disproportionate to what has been demonstrated objectively, attention should again turn to environmental or extra-pulmonary factors that might be relevant and modifiable (tables 5 & 6).

This strategy recognising 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 given patient and may change over time, either as a part of the natural history of the disease and/or as a consequence of therapy. Importantly there is no assumption of a causal link between one component and another. The strategy encompasses overlapping disorders, comorbidities, environmental and life style 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 approach and we would hope they are refined and more specifically targeted to more

clinically important mechanisms with time. So, with the advent of ever more monoclonals, we need to move beyond cell based definitions to pathway based definitions, particularly in non-eosinophilic airway diseases. Although not definitive, there is already consistent evidence that the sort 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[10,11,24,25,162,163]. Additional strengths of this proposal are[118]:

(1) specific diagnostic criteria for the components are proposed, and expected treatment benefits outlines, in terms of patient relevant and surrogate outcome measures (Table 4-6);
(2) it recognises that different components relate particularly to different aspects of the clinical problem or future risks (i.e. eosinophilic airway inflammation and the risk of attacks);
(3) it may be cost-effective because of more economical use of treatment and the expected larger therapeutic response;
(4) it can stimulate best translational research by identifying knowledge gaps;
(5) it can help to identify key inclusion- exclusion criteria for future randomized clinical trials.
(6) it can be applied in any patient with airway disease leading to more precise therapy, rather than ~~a~~ label and one size fits all approaches;
(7) it 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.

~~Figure 5 illustrates how the categorisation of patients on the basis of the dominant treatable traits might lead to a better targeted treatment. This theme is developed in the next section.~~

SECTION 2: BEYOND GUIDELINES. OPERATIONALISING INDIVIDUALISED TREATMENT IN DIFFERENT HEALTH CARE SETTINGS

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

The rise and fall of guidelines

The paradigm for the management of asthma, hallowed by numerous international guidelines, is a one size fits all stepwise approach according to the level of asthma control (figure ~~5~~5). This basic construct has not changed much since the first guidelines were published ~~25~~ 27 years ago[14-17]. Current treatment is initiated with an inhaled SABA as required in intermittent asthma, with the addition of maintenance low dose ICS in mild persistent asthma, and then stepping up to combination ICS/LABA therapy in moderate asthma, with the dose of ICS in the combination inhaler

increased in severe asthma to obtain control. This control-based management approach means that treatment 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 stepped care works well when dealing with a homogeneous well-defined condition, when treatment responses are relatively consistent between patients and across different outcomes, and when the goals of management are realistic and achievable; and indeed for many patients guidelines stressing anti-inflammatory therapy have brought substantial benefits. However, as is apparent from the sections above, neither of the first two criteria are met in the whole gamut of 'asthma'. Perhaps we have jumped headlong into the guideline production business without establishing first whether the entity whose management we are seeking to guide is ~~a~~ useful and sufficiently well ~~-~~defined ~~construct~~[22]. ~~In~~ An additional problem is that~~,~~ the goal of treatment – to eliminate symptoms and attacks and to normalise lung function – may well ~~not~~ be unachievable in a significant proportion of patients[164,165]. One result of this is to drive treatment requirements (and cost) up in a spiralling manner. ~~Treatment decisions at different steps are over-generalised, resulting in illogical treatment in significant numbers of patients. For example, the addition of LABA is recommended in patients whose condition is uncontrolled by low dose ICS, yet is this the best option for a patient who has evidence of active eosinophilic airway inflammation and whose dominant clinical problem is recurrent attacks? What is needed is to identify those patients who do not respond to the initial approach suggested in figure 5 and move on to precision medicine rather than blindly following the standard step-up treatment plan.~~

The providence, scope and ~~method of development~~proliferation of modern guidelines have all led to problems. By necessity ~~this~~guidelines result~~s~~ in recommendations that are conservative and based on evidence from randomised controlled trials carried out in well-defined but poorly generalisable populations[166] Treatment decisions at different steps are over-generalised, resulting in illogical treatment in significant numbers of patients. For example, the addition of LABA is recommended in patients whose condition is uncontrolled by low dose ICS, yet is this the best option for a patient who has evidence of active eosinophilic airway inflammation and whose dominant clinical problem is recurrent attacks? What is needed is to identify those patients who do not respond to the initial approaches suggested in figure 5 and below and move on to precision medicine rather than blindly following the standard step-up treatment plan~~.~~. ~~An additional difficulty is because guidelines have become much more than recommendations and are increasingly seen as unchallengeable dogma~~. Early asthma guidelines produced evidence on a few core concerns for diagnosing and treating the

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condition. We have since seen lengthening of guidelines ~~has~~ resulting~~ed~~ in ~~–~~important recommendations being lost amongst minor self-evident ones. Increasingly guidelines are used to establish medical and legal standards of care resulting in recommendations that become set in stone ~~and difficult to modify~~, making it difficult to innovate and generate new evidence. Finally, a profusion of different guideline groups have emerged over the last 20 years leading, in some cases, to variable recommendations. Box ~~3~~5 summarises the views of a number of influential guidelines on the use of FeNO to guide diagnosis and management of asthma ~~management~~. This conflicting and confusing advice occurs because different questions were a~~ddressed~~sked. The 2016 GINA[87] and 2014 BTS/SIGN[167] paediatric guideline groups asked: how valuable is FeNO in supporting a diagnosis of asthma? They ~~and (right~~correctly~~ly)~~ concluded that it was not helpful. In contrast the 2014 BTS/SIGN[167] adult and 2011 ATS clinical practice guideline[168] ~~asked~~groups came to a very different conclusion in response to a more specific question which did not pre-suppose that 'asthma' was a useful entity: which test best identifies eosinophilic airway inflammation and corticosteroid responsive airway disease?~~.This is a problem when recommendations may be influenced unduly by expert dogma.~~

Asthma management in low and middle income countries

Poor precision of treatment and spiralling treatment costs are an important issue in low and middle income countries (LMIC) where tools required for diagnosis and effective inhaled therapies are routinely unavailable and/or unaffordable. Simple tests such as spirometry may have more utility in this setting as diagnostic overlap with respiratory infections or other chronic respiratory diseases occurs more commonly. Poor availability may therefore be a factor leading to diagnostic error and potentially under diagnosis. There is a lack of implementation of what would be regarded as standard care in high income places. The unacceptable inequity that still exists globally regarding asthma diagnosis and management and the collision of two worlds – in one where talk is about precision medicine and need for individualised phenotyping to guide diagnosis and management and in the other where there are not even basic tools for diagnosis and management ~~–~~ presents considerable challenges. We need to keep in mind that the predominant childhood population and a substantial adult population is in LMICs, so addressing the challenges of diagnosis and management in these settings will have a large impact, and if inhaled beclomethasone, inhaled salbutamol, prednisolone and a milk bottle spacer were available to all, the global impact would be huge[169].

Where do we ~~think we~~ want to go?

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Move from one size fits all management to precision medicine

First and foremost, we need new approaches which deconstruct airway disease in all those who do not respond to the initial treatment recommendation. The key limitation inherent to the paradigm of the 'one size fits all' guideline-based approach to asthma management, based on ICS and beta 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[72,81] (table 4), and so a precision approach would seem more logical. For example, this may avoid both inappropriate 'overdosing' of ICS in symptomatic patients with non-eosinophilic asthma, including the obesity-related phenotype[23,115], inappropriate 'undertreatment' with ICS in patients with severe eosinophilic asthma, as well as inappropriate overdosing with maintenance LABA therapy in asymptomatic patients with relatively fixed airflow obstruction.

The precision approach we advocate addresses the increasingly recognised conundrum regarding the treatment of patients with the poorly defined asthma/COPD overlap syndrome, in which undue emphasis on the COPD component could lead to risks of sole bronchodilator LABA and/or LAMA therapy, or undue emphasis on the asthma component which may lead to unnecessary side effects from ICS therapy and inadequate bronchodilator therapy. This problem (and the ACOS and COPD acronyms) disappears if the airway disease in the individual patient is deconstructed, and treatable traits treated, without worrying about diagnostic silos.

A related issue is whether alternative treatments to ICS and β_2-agonists may be preferable in selected patients. Specific 'responder' groups have not been identified for established treatments such as Theophylline, leukotriene receptor antagonists (LTRA) and long-acting anti-muscarinic agents (LAMA), or potential treatments directed against latent infection or anti-oxidant stress. The further investigation of pathways and hence biomarkers to identify responder groups to therapeutic agents similar to the approach used with ICS 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 that make up the spectrum of asthma (see section 4).

Smarter monitoring and new treatment paradigms

Recommendations regarding monitoring of the asthma patients are unfortunately often also of the 'one size fits all' type. Should the monitoring approach be tailored to the specific phenotype of the patient? Monitoring should be considered as an iterative and adaptive process, whereby changes in

the phenotype, drug response, adherence, developmental aspects in children and disease stability are constantly re-assessed (see figure 6). Patient's individual behaviour in the past should be considered by the physician for treatment decision making.

Once established on treatment, monitoring is an iterative process where symptoms and risk of adverse outcomes (i.e. attacks) are assessed and management fine-tuned. As symptoms due to airflow limitation and risk as a result of active eosinophilic airway inflammation are currently by far the most important and recognisable treatable components in patients with airway disease, the schema set out in figure 6 would be sufficient in most circumstances and should be applicable in primary care and other non-specialist settings[170]. 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 discussed in tables 4-6. Two immediately obvious scenarios are the patient with symptoms not due to airflow limitation and a patient with recurrent exacerbations with low biomarkers of eosinophilic airway inflammation. Cough reflex hypersensitivity is an important cause of the former and infection-related neutrophilic airway inflammation of the latter. One advantage of the approach outlined above and in figure 6 is that these possibilities become apparent early on in the diagnostic process rather than after many months of fruitless and escalating inhaled treatment.

~~An important aspect of asthma management is proper use of medication delivery devices and adherence. In this context, the continued, widespread use of metered dose inhalers without spacers is a manifestation of truly impressive complacency, given how easy it is to use them wrongly, and how inefficient they are even when used correctly. We accept that metered dose inhalers when used with spacers have a role in the very young (less than 3 years), the elderly with coordination problems, those who need high doses of ICS (likely far fewer numbers than those prescribed them!) and possibly in LMIC settings for financial reasons, but at the very least they should be modified so as only to be able to be activated when attached to a spacer. If adherence is to be tackled, we need to have devices that detect not merely activation but also inhalation and its adequacy, and feed this back day by day to the patient and the physician, with alerts when medication is not taken. Futuristic? The Hubble telescope can beam images from the edge of the known universe down to earth, and yet those of us treating a life threatening disease are content to use old fashioned technology to deliver medications. Small wonder that we do not use the medications we have effectively!~~

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Finally, in considering asthma management in its broader context, ways to enhance the patient/healthcare 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[87]. One of the important concepts of asthma 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, out patient consultations have not changed in over a century; an unruly scrum waiting to be seen, a brief face to face consultation with someone with a medical degree and variable knowledge of the patient and the disease, who may or may not have access to the previous notes, then summary ejection until it is time for the cycle to repeat itself. The challenge now exists to utilise advances in information technology and communication, which have been underutilised in the past, to improve such partnerships in an evidence-based and cost-effective manner. The young use social media to communicate many times a day; why do we not use this in health care? It is possible to use a smartphone APP to monitor how many steps someone has walked in a day; why do we not use APPs to monitor airway disease continuously and in real time, obviating the need for patients to perceive symptoms? There is already evidence that this sort of approach works[171] and even in LMICs, many have smartphones – can these not be utilised to improve access to health care?

Recommendations regarding monitoring of the asthma patients are unfortunately often also of the 'one size fits all' type. Should the monitoring approach be tailored to the specific phenotype of the patient? Monitoring should be considered as an iterative and adaptive process, whereby changes in the phenotype, drug response, adherence, developmental aspects in children and disease stability are constantly re-assessed (see figure 6). Patient's individual behaviour in the past should be considered by the physician for treatment decision making, whereby modern electronic monitoring techniques may play a more important role in the future.

Several randomised controlled trials have shown that the precision medicine and smarter monitoring approach ~~to treatment~~ in adult asthma outlined above is superior to conventional stepped therapy in well-resourced countries[10,11,24,25]. In LMICs, the first priority is to get basic therapy available in every community (figure 5). When this has been achieved, we suggest that the approach illustrated in figure 6 is likely also to be useful although could be adapted to this setting. It should be noted that our proposed approach does not make the assumption that asthma in Africa is the same as in London; indeed, given the much greater and more disparate burden of childhood infections in LMICs, they may be very different[172,173]. This is another problem in the use of umbrella terms across the globe; it is so easy to slip into the assumption without even noticing this has happened. For example that the disease is the same ~~for example~~ in Paris and Paraguay, and that what works in Paris should be uncritically deployed in Paraguay

There are, however, several important unresolved issues. One key question is how 'stable' are the eosinophilic and non-eosinophilic asthma phenotypes and whether simple biomarker assessments (e.g. blood eosinophil and FeNO, which are predictive of a response to ICS) will consistently identify these groups[174]. The related clinical question is whether ICS can be safely withheld in patients with a specific biomarker profile. This highlights a key feature of the proposed paradigm: the need for stratification in planning treatment. Some patients with objectively documented episodic asthma may be eosinophilic at one point but not at another[175] but it might be difficult to distinguish true 'episodic asthma' and 'episodic symptoms with unrecognized persistent airflow limitation or inflammation' without repeated objective evaluation. Overestimation of control and difficulty understanding symptom patterns over time might present additional difficulties, particularly in paediatric care, where the history is primarily obtained from a third-party (parents) or reported by children. The pragmatic solution may be to use intermittent and/or regular low dose ICS/SABA or fast onset LABA/ICS combination therapy in such patients as discussed below.

The second key question is what to use instead of escalating doses of ICS in patients with non-eosinophilic obstructive airway disease. LABA monotherapy has been shown to increase the risk of mortality in patients with asthma[176]. Whilst it may well be the case that this risk is exclusive to patients with an eosinophilic- pattern of disease, it would be difficult to prove this definitively. We therefore suggest that as required ICS/SABA or fast onset LABA/ICS combination therapy is the default position in patients with variable symptoms and/or airflow limitation, but that ICS dose is not escalated unless biomarkers of eosinophilic airway inflammation are raised (figure 6). Long-term low dose macrolide antibiotics have been shown to be effective in small studies of non-eosinophilic

asthma[141,142], but patient side effects and concerns about global antibiotic resistance limit their widespread use. The use of alternative treatments such as Theophylline, Leukotriene receptor antagonists (LTRA) and Long-acting antimuscarinics (LAMA) has not been examined in detail in this patient group so it is difficult to make specific recommendations. The weakness of all these suggestions is that they lack a satisfactory evidence base; we urgently need to understand pathophysiology and pathways as a basis for management approaches which are assessed in RCTs, if we are going to offer these patients 21st century care rather than firing treatments at them with the current scattergun approach.

Crucial to the current approach is the validity of the 'cut-points' at which prescribers and patients move up or down to the next step in treatment. Arguably the most important step is when low dose ICS are prescribed, a therapeutic approach which previous guidelines have recommended when patients use their SABA on more than two occasions per week[86], and more recently (based on ~~preliminary~~ growing evidence), on two or more occasions per month[87,177]. However, international surveys have shown that doctors do not recognise the need for ICS therapy at such stages[178] and there is a tendency for patients and clinicians to overestimate control. Furthermore, if prescribed, adherence to ICS may be as low as 20%, which is not surprising as patients are required to take twice daily treatment regardless of whether they have symptoms[179]. Recognition by primary care practitioners that patients with intermittent and/or mild asthma are unlikely to be adherent with regular ICS treatment may make them reluctant to issue a prescription. However, poor adherence is associated with significant asthma-related morbidity, and there is a greater than three-fold increased risk of an asthma exacerbation after stopping low dose ICS[180].

Recognition of this conundrum has led to consideration of methods that are applicable in primary care, which may improve ICS adherence, as well as alternative regimens to that of sole SABA therapy for symptomatic relief in intermittent asthma. The biomarker directed approach suggested in figure 6 might help clinicians to make a definitive treatment decision and encourage patients to commit to that treatment. The current first step is use of SABA as required; this is only logical if what is treated is intermittent constriction of airway smooth muscle. If in fact there is concomitant, albeit low-grade eosinophilic inflammation, should this not also be treated, perhaps using a combination ICS/fast-onset β_2- agonist inhaler solely as reliever therapy? Stated in these terms, the absurdity of the current debate between these two options as step 1 is manifest; what is needed is not a sterile debate about possibilities, but measurements of the problem and precise treatment, even for apparently mild disease. There is a substantial rationale for a regimen that utilises symptom-driven

β_2-agonist use as the vehicle for ICS delivery and allows self-titration of ICS dose according to changes in asthma control[9]. However, this approach (as do so many current paradigms) 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 in adults with intermittent and mild asthma has shown that the symptom-driven use of combination ICS/SABA medication achieves similar efficacy to regular ICS therapy, and leads to fewer severe exacerbations compared with sole SABA reliever therapy[181]. In children, the TREXA study showed that, in the phase of weaning down treatment, intermittent combined ICS/~~LABA~~ SABA were more effective than ~~LABA~~ SABA alone, and had fewer side-effects than continuous low-dose ICS albeit at the expense of slightly lower lung function[182]. As there is no place for treatment with LABA monotherapy in asthma (perhaps particularly in those with eosinophilic airway inflammation), we should question the use of SABA monotherapy in mild asthma of this phenotype. Further investigation of ICS/SABA and ICS/fast-onset LABA reliever therapy for intermittent and mild asthma represents a priority and will determine whether single inhaler therapy may be possible across the spectrum of asthma severity, initially with a single ICS/fast-acting β_2-agonist inhaler used as reliever therapy only, then progressing to its use as both maintenance and reliever therapy (MART).

From a therapeutic perspective, ICS/fast-onset LABA therapy prescribed according to the maintenance and reliever regimen reduces the risk of severe attacks by about 40 to 50% compared with prescribed maintenance ICS/LABA and SABA reliever therapy, despite similar efficacy for other outcome measures such as lung function and asthma control[183,184]. Efficacy of this approach, and of a biomarker directed approach, is particularly obvious during times when the risk of attacks is increased[185] and perhaps in poorly adherent patients[186]. This evidence underlies the preferred use of ICS/fast-onset β_2-agonist therapy (prescribed as needed or according to the MART regimen) in patients requiring therapy for documented episodic disease. Since the MART approach is based upon the hypothesis that an increase in asthma symptoms is due to increased eosinophilic airway inflammation, which responds well to additional doses of ICS within the ICS/fast-onset LABA reliever, this approach may be most applicable in patients with eosinophilic asthma. However, it would be difficult to identify with confidence a population of patients in whom ICS can be safely withheld and we believe that it would be reasonable to adopt this approach generally.

Better appreciation of the dose-response relationship with ICS

There is also a need to revise the current guidelines classification of low, moderate and high daily doses of ICS. In adults the current classification that low doses are represented by fluticasone

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propionate (FP) doses of 100 to 250µg per day is not based on evidence that 90% of the maximum obtainable therapeutic benefit is achieved at an FP dose of 250µg per day[187], or the lack of greater efficacy with initiation of ICS therapy at daily doses above 400µg budesonide or equivalent[188]. In children, the BADGER study showed that few improved when the dose of FP was increased above 100 µg bd[189]. Further investigation of the ICS dose-response relationship for both efficacy and systemic adverse effects is required, particularly in children. However, there needs to be an appreciation that this plateau may well be dynamic. So if there is a considerable pro-inflammatory drive - for example from exposure to aeroallergens to which the patient is sensitized and cannot avoid - then there may be relative steroid resistance leading to the requirement for larger and more frequent doses of ICS [190]. This underscores the value of the approach described in section 1 to not consider airway disease in isolation, but also in the context of the environment. Interestingly, systemic absorption of high dose ICS is less in those with inflamed airways[191], which may 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 may be so high that even small changes in recruitment signals in the airway lead to important worsening of airway inflammation. This possibility is supported by the beneficial effects of depletion of circulating eosinophils with anti-IL-5, and the very close relationship between clinical benefit of treatment and the pre-treatment blood, but not sputum, eosinophil count[12]. If this model is correct then it is not inconceivable that any benefit of very high dose ICS is a direct result of systemic activity and could be achieved more cheaply and just as safely with a small dose of oral corticosteroids.

Better technology

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An important aspect of asthma management is proper use of medication delivery devices and adherence. In this context, the continued, widespread use of metered dose inhalers without spacers is a manifestation of truly impressive complacency, given how easy it is to use them wrongly, and how inefficient they are even when used correctly. We ~~accept that metered dose inhalers when used with spacers have a role~~propose that beyond the use of metered dose inhalers with spacers in the very young (less than 3 years), the elderly with coordination problems, those who need high doses of ICS (likely far fewer numbers than those prescribed them!) and possibly in LMIC settings for financial reasons, ~~but at the very least they should be modified so as~~a case can be made to ensure universal use through their modification so that they can only ~~to be able to~~ be activated when attached to a spacer. If adherence is to be tackled, we need to have devices that detect not merely activation but also inhalation and its adequacy, and feed this back day by day to the patient and the physician, with

alerts when medication is not taken. We need research to better understand patients' responses to these devices and this type of monitoring. Futuristic? The Hubble telescope can beam images from the edge of the known universe down to earth, and yet those of us treating a life-threatening disease are content to use old-fashioned technology to deliver medications. It is salutary to reflect on the differences between the Bakelite dial telephone of twenty five years ago and the modern Smartphone, during which time progress in metered dose inhaler technology has been exactly zero. Small wonder that we do not use the medications we have effectively!

Although we argue against individual therapeutic trials as a basis for long-term treatment decisions, it is an unpalatable fact that currently these are inevitable in at least some contexts, e.g. pre-school wheeze. However, we can progress beyond giving an inhaler and asking if it worked after a six-week trial. There is no reason why these N-of-1 trials cannot be placebo controlled, double blind and incorporate electronic monitoring of adherence, including technical adequacy of the inhalation technique.

21st century asthma clinics

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Finally, in considering asthma management in its broader context, ways to enhance the patient/healthcare 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[87]. One of the important concepts of asthma 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, out-patient consultations have not changed in over a century; an unruly scrum waiting to be seen, a brief face to face consultation with someone with a medical degree and variable knowledge of the patient and the disease, who may or may not have access to the previous notes, then summary ejection until it is time for the cycle to repeat itself. The challenge now exists to utilise advances in information technology and communication, which have been underutilised in the past, to improve such partnerships in an evidence-based and cost-effective manner. The young use social media to communicate many times a day; why do we not use this in health care? It is possible to use a smartphone APP to monitor how many steps someone has walked in a day; why do we not use APPs to monitor airway disease continuously and in real time, obviating the need for patients to perceive symptoms? There is already evidence that this sort of approach works[171] and even in LMICs, many have smartphones – can these not be utilised to improve access to health care?

~~The precision approach we advocate addresses the increasingly recognised conundrum regarding the treatment of patients with the poorly defined asthma/COPD overlap syndrome, in which undue emphasis on the COPD component could lead to risks of sole bronchodilator LABA and/or LAMA therapy, or undue emphasis on the asthma component which may lead to unnecessary side effects from ICS therapy and inadequate bronchodilator therapy. This problem (and the ACOS acronym) disappears if the airway disease in the individual patient is deconstructed, and treatable traits treated, without worrying about diagnostic silos.~~

~~A related issue is whether alternative treatments to ICS and β_2 agonists may be preferable in selected patients. Specific 'responder' groups have not been identified for established treatments such as Theophylline, leukotriene receptor antagonists (LTRA) and long acting anti muscarinic agents (LAMA), or potential treatments directed against latent infection or anti oxidant stress. The further investigation of pathways and hence biomarkers to identify responder groups to therapeutic agents similar to the approach used with 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 that make up the spectrum of asthma (see section 4).~~

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SECTION 3: WHEEZING ILLNESSES ACROSS THE AGES

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

The evolution of airway function between the first and tenth decade has been described by curves produced from nearly 100,000 cross-sectional observations. It is clear from these and other data that there are three key places that can impact on long-term risk of airways disease. The first is to ensure normal lung function at birth - abnormal birth (or at least, pre-school) lung function tracks into the third decade at least; ~~–~~the second is to ensure normal growth in lung function during childhood until to a plateau is reached at age 20-25; and the third is after this age, when accelerated decline leads to low lung function in later life.

A large number of overlapping birth and other cohorts have been studied, in some cases with follow up over many decades. These have taught us that, in chronological not discovery order:

- Transgenerational factors (grandparental smoking) impact on risk of airway disease[127]
- Antenatal factors such as exposure to tobacco smoke[135] and pollution[133] impact airway disease in the foetus in three main ways: (a) by an effect on gestational age and birth weight; (b) by direct effects on lung structure; and (c) by effects on the foetal immune system leading to abnormal responses to allergens and viruses[134]
- Place (home vs. hospital[192]) and mode (vaginal vs. Caesarian section[56]) of delivery may impact the risk of future airway disease
- In the immediate post-natal period, there is further loss of lung function in those who develop persistent wheezing illnesses, in particular if there is neonatal airway hyper-responsiveness[59]
- 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[63,193,194].
- Postnatally, passive smoking[55], pollution[133], moisture damage[195], obesity[196], pesticide exposure[197] and multiple early atopic sensitization[64,66] 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 later COPD[126].
- Spirometry tracks over many decades; under most circumstances there is no catch-up lung growth[129]

- Airway disease in pre-schoolers may recrudesce after quiescence in adulthood or manifest for the first time in adulthood[50]
- Adolescent girls with premature menarche ~~are~~ may have an increased ~~at~~ risk of developing asthma[198].
- There appear to be multiple trajectories to 'COPD'. In a recent longitudinal analysis showed that of those with an FEV1 is ≥ 80% in early adult life, 158/2207 (7%) had a fast decline in spirometry and developed COPD. Another group had a FEV1 < 80% in early adult life, and 174/657 (26%) developed COPD; they had normal rates of decline in spirometry. Both trajectories contributed equally to the burden of COPD, although clearly they differ in the rate of decline in lung function in later life[129]. Subsequently, follow up of the CAMP study bridged the gap between adult and childhood studies[199]. There were four asthma spirometry trajectories, comprising combinations of normal or reduced plateau of lung growth, and normal or early decline in spirometry, independent of treatment prescribed (nedocromil, budesonide, placebo).
- In the many large studies of rate of change of spirometry in adult life[200-203] no single environmental factor, including smoking, consistently predicts an accelerated decline.

In early life, we must move on from irrelevant questions like 'at what age can we diagnose asthma?' (which, as we argue above, is neither a single diagnosis nor an intelligent question) and instead, think about the treatable traits of airway disease[53]. So in early life, we still quarrel about what is bronchiolitis and what is viral wheeze, and what is asthma without defining our terms clearly, and worse still, have no biomarkers to differentiate them. We know that viruses are an important trigger of attacks of wheeze[152,153], but we have assumed that all viruses are equal, and equally treatment resistant, on the basis of limited data[204]. We know that children with eosinophilic airway inflammation and variable airflow obstruction at school age had airflow obstruction at birth and/or during early life[59]; but other than tackling tobacco smoke and pollution (in a half-hearted manner) we don't know how to prevent this. We know that aeroallergen sensitization (in particular, multiple early sensitization) in the same time period is associated with ongoing symptoms and loss of lung function and persistent airway hyperresponsiveness[64], but we don't know how to prevent this either, this despite knowing that airway function tracks from the pre-school years to late middle age, so the pre-school years are critical. We cannot prevent early viral infections like Rhinovirus or Respiratory Syncytial Virus (RSV) in most children, ~~although~~ and current work ~~in~~on ~~-~~the development of ~~a~~ anti-RSV ~~vaccine~~ approaches ~~is encouraging~~has produced mixed results[205,206]. We have also become bogged down in irrelevant questions like 'do children with sickle cell

disease/bronchopulmonary dysplasia/other causes of wheeze have 'asthma', instead of trying to determine the specific nature of their airway disease in terms of the traits shown in table 4.

Current knowledge of the developmental trajectories of asthma is limited. A number of prospective cohorts have established patterns of wheezing going forward from infancy; and largely from a series of overlapping cohorts, the significance of early wheeze has been determined in adult life (see above). However, these studies are in large populations, and by definition are non-invasive, and hence tell us little or nothing about the developmental changes in mechanisms. For example, the assumption is made that atopy-associated asthma in school age is driven by the same pathways as in adults; but there is at least some evidence that in severe asthma, the innate epithelial cytokines and lineage negative innate lymphoid cells may be more important in severe asthma in children than in adults[207]. Furthermore, classical adult asthma phenotypes and complications (aspirin sensitive asthma, allergic bronchopulmonary aspergillosis, occupational asthma, late onset asthma) remain in adult silos, with largely very little attempt to understand whether they have their roots early on; this despite the clear demonstration[208] that women with so-called 'late-onset asthma' actually had significant symptoms (long forgotten) and physiological abnormalities in early life! Indeed the very term 'late-onset' pre-judges the issue, and discourages any thinking about probable early roots.

We know that recall of even major childhood respiratory illnesses (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 adult life interviews[208,209]. In the context of interstitial lung disease, we can clearly see that the same gene mutation (SpC) in the same kindred can cause very different diseases (neonatal pulmonary alveolar proteinosis[210], adult onset pulmonary fibrosis[211]), presumably related to modifier genes and environmental exposures. There is animal evidence that transient exposures during key time windows (e.g. neonatal hyperoxia[212]) may affect responses to allergens and viruses in adult life. So it is at least conceivable that some of the adult phenotypes which we think we do not see in childhood are in fact manifestations of something causing a very different early airway disease. These age windows may be a key opportunity for disease modifying treatment or primary prevention strategies. It is highly unlikely that there will ever be a big enough birth cohort to study these relatively uncommon adult phenotypes prospectively, (and even if one is started, it will only be of interest to our professional grandchildren) so a different approach will be needed.

The evolving picture of airway disease is characterized 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, if they exist, are as yet unknown. Li et al[213] have postulated that small risks may 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 given risk allele might be magnified by an adult life exposure, for example occupational, or become relevant during lung aging, for example impaired pre-school airway development.

The development of the respiratory system in early childhood is complicated, however, by growth processes and adaptation to changing environments, including going from intra-uterine to extra-uterine. Complexities also occur in the aging adult as a result of age-related senescence. While some outcomes may be the result of a cumulative effect, complexity theory suggests that these mechanisms and interactions are likely far more complex, non-linear, and they remain not merely largely unknown, but not even considered. Interactions can only be hypothesized based on general principles inherent in complex systems biology, such as degeneracy[214]. Degeneracy in systems biology refers to the ability of alternate structural pathways to exhibit similar or dissimilar functional outcomes depending on context. Frequently mislabelled redundancy, degeneracy refers to structural variation whereas redundancy refers to structural duplication. Degeneracy has been described in the immune system[215], the control of breathing[216], and human movement analysis[217]. For adaptive, complex systems, degeneracy has several benefits - e.g. it improves robustness to perturbation by, for example, an environmental stimulus and allows for adaptability[218]. In the developing respiratory system, complex behavioural adaptations may be necessary in order to adapt to changing environmental conditions from foetus to adulthood. Given such phenomena, the overall asthma risks may 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 may have contributed to the evolution of a greater heterogeneity of phenotypes than has previously been considered, given 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 7 shows recognised wheezing syndromes by age, with suggested major treatable traits. Machine learning approaches have been fruitfully

applied to the study of atopy[67,219], once considered an 'all or none' phenomenon. In fact, only the latent class of early multiple atopic sensitization (but not any other sensitisation classes) in the Manchester and Isle of Wight studies[67,219] was associated with a worse trajectory of lung function, in particular if associated with acute attacks of wheezing[51]. It is very clear that the complexities of asthma trajectories cannot be described in simple terms, or by single cross-sectional measurements, and that conclusions drawn from cross-sectional analyses of longitudinal data may not accurately reflect longitudinal trajectories within individuals[220]. Moreover, while 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 may or may not apparently resolve), and in others health is maintained. It is likely that several sub-systems are involved in this complex disease, interacting in a network-type manner. These sub-systems or "compartments" include, 'lung growth and structure', 'innate immunity' (viral infections, mucociliary clearance, surfactant, toll-like receptors, etc.) and 'adaptive immunity' (IgE/G_4; response to infections), 'allergic sensitization', 'epithelial function (barrier and secretory)', 'oxidative stress response', 'remodeling and repair mechanism', 'smooth muscle function', 'metabolic rate and nutrition', 'interaction with the microbiome', and many others.

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Notably, all of these compartments are influenced by specific genomic and epigenomic regulators, and are similarly altered by environmental factors which may be specific to that compartment[221]. Genomic and epigenomic changes have not only been associated with atopy and asthma, but also amongst other factor with airway smooth muscle function, lung function, glucocorticosteroid response, effects of prenatal tobacco exposure, air pollution, prenatal sensitization, stress[222] and viral infections[223]. Based on these considerations, future asthma models need to consider not only developmental gene-environment interactions of the organism, but also those of each compartment, as well as 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 given polymorphism may be age-dependent and be different with different environmental exposures[65]. Gene expression and epigenetic regulation change by age, and can even be induced during pregnancy[224]. The relative importance of innate and adaptive immune response drastically changes in the first year of life in response to environmental antigens and also in the context of asthma[63,225,226].

The dominant maturational changes in each compartment or subsystem of the body take place at different times. For example, airway size and lung volumes increase until adolescence, whereas the development of the immune system, or the stabilization of the gut microbiome[227], is complete in early childhood (Hypothesis 1: Figure 8). Consequently, if asthma is considered a network response of many weak effects in all of these compartments, their relative contribution, or their susceptibility to environmental stimuli, likely also changes with age (Hypothesis 2: Figure 9). Age-dependent effects of risk factors on respiratory symptoms has have been demonstrated, for example, in the case of tobacco smoke exposure[228], immigration studies[229] and farming exposure[230]. Maturational programming is likely to be determined by the interactions between intrinsic (e.g. growth processes) and extrinsic factors. The system adapts, 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 result is the given compartment 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 recent model has suggested that the gene-environment interaction determines the asthma phenotype in early childhood[231]. It is likely that the relative contribution of a specific compartment could become dominant at a given age, and could determine the phenotype. Our hypothesis (Hypothesis 3: Figure 10) is that the evolution of asthma may be an aberration of one or many different interacting compartments. The compartments involved in the transient wheezing phenotype may include, among others, airway size and innate response to viral infections. In contrast, persistent wheeze may be an early aberrant stabilization in response to disease, which may impede subsequent healthy maturation. Intermittent phenotypes may manifest as changing states of stability in response to environmental exposures or unrecognised persistent disease between attacks.

Where do we ~~think we~~ want to go?

Cross-sectional studies cannot study asthma disease trajectories. Future studies would thus need to assess key compartments of the disease process with a multi-dimensional or even multi-level (gene-molecule-cell-organ) approach, as well as the interaction between them and quantify their relative contributions. We need to know how the genes and environmental factors affect the key compartments that lead to cumulative or even critical effects in the context of development. Such

network type analyses are well known in systems biology. We thus need a step change in longitudinal studies, using well-defined outcomes reflecting the various compartments (lung function, immunological, inflammatory, metabolic, genetic, epigenetic). Furthermore, systems medicine often neglects the idea 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, it is critically important to quantify and characterize the individual's response to the exposome (i.e. every exposure to which an individual is subjected from conception to death)[232]. This is an example where if paediatricians emerge from their silo, they can learn a lot from adult Occupational Health physicians.

Clearly even if a new birth cohort study addressing 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! So we need to use existing longitudinal and also cross-sectional studies innovatively. For example, a detailed biological signature of the rapid decliners in adult life[129] should be compared with the same parameters earlier in life, to determine whether this group can be detected early, at a time when (perhaps) an intervention can abort later deterioriation. One example is serum CC16, which is associated with reduced lung function in childhood, and accelerated lung function decline in adulthood[233]. This can be a two way process – are early biological phenotypes and signatures associated with later phenotypes? So some cohorts had no early microbiome studies, but they could obtain late middle age samples, which could be compared with those of cohorts in childhood and early adult life, as well as being explored in animal models. This is not the scientific ideal, but until time travel becomes an option, it is a pragmatic approach to understanding longitudinal biological complexity.

To develop preventive strategies we have first to understand the pathways whereby early life events effect lung function in the long term. We need to identify factors that prevent or reverse adverse changes, and the understanding of normal lung development may be a prerequisite. Basic science could help by developing better animal models with long-term observations in the growing animal and studies looking at the interactions of a multitude of small triggers, rather than single e.g. house dust mite exposures (see below); and epidemiologists and basic scientists need to emerge from their silos to co-design these models. These models need to use network-type analyses to assess the key compartments and pathways, their interactions and their relative contributions and how these result in cumulative or even critical effects during various phases of development.

If these ideas are correct, epidemiological studies need to be taken to a whole new level of complexity. 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 by environmental interactions, that is acceptable in big, longitudinal, population based studies. The challenge is also to mine existing cohorts for data that may be used to show insights into these complexities; in this context, the harmonization of cohorts into big data sets, such as the STELAR e-lab[234], are particularly welcome. We also should lift our eyes from a pulmonary focus, and consider whether other organs (e.g., the cardiovascular, endocrine, metabolic and/or neurologic systems) might have also suffered similar developmental abnormalities[235]. We know that trivial decrements in lung function and birth weight are associated with disproportionately increased mortality rates. Are they canaries in the mine for the whole body?

From a clinical perspective we have been blinkered into honing down onto the immediate disease manifestation, and failed to ask three basic questions:

- What was the developmental trajectory to the current status?
- What are the current components of the airway disease (section 1)?
- What will be the onward developmental trajectory from here?

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

SECTION 4: ~~TREATMENT OF THE ASTHMAS~~BEYOND PALLIATIVE CARE – TOWARDS PREVENTION AND CURE

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

The standard answer to the question of what constitutes the greatest unmet need in asthma almost invariably highlights the requirement for more effective therapeutics for patients with chronic asthma who are refractory to currently available treatments. While this understandably resonates with treating physicians and their patients, its blanket acceptance as the number one priority across a wide segment of the asthma research community, and amongst drug developers, health care providers and regulatory authorities, serves to perpetuate what has become the *status quo* in developed (and increasingly in developing) countries: the inexorable progression from intermittent early childhood wheeze to persistent asthma in the teen years, and thence to an ensuing life sentence of therapeutic drug dependence[236]. From a public health perspective the answer to the

same question is of course radically different: "the lack 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 bear some responsibility for the low priority afforded to primary prevention strategies. By jumping straight to established asthma, and not considering the fundamental underlying causes, they have set the agenda for asthma as a disease to be controlled not cured, without apparently focussing on at least trying to devise strategies to intervene early to prevent progression to this state.

Hence it is unsurprising that disease control-based care has informed much so called 'innovation' in asthma. The focus has been on newer and more potent ICS and once daily LABAs, which can be characterised as merely more of the same. Do we really *need* another ICS? Should NICE and other regulatory authorities put a blanket ban on licensing any new ICS or LABA unless they are cheaper than and at least as effective as what we have already? ~~Furthermore, it is becoming clear~~We also need to be aware of the possibility that increasingly potent ICS may be harmful. The airway mucosa has and requires sophisticated immune defence mechanisms against pathogens and other inhaled irritants and ICS increase the risk of pneumonia, tuberculosis, and atypical *Mycobacterial* infection[103]. ~~Yet newer more potent ICS are appearing on the market!~~

These new ICS have led to spiralling costs of asthma treatment which seem set to continue rising despite evidence of diminishing returns[19]. Are the newly formulated inhaled corticosteroids really any better than Beclomethasone? Some of us have argued before[236] that the continuation of this trend is inevitable unless there is a substantial realignment of entrenched drug development policy in the pharmaceutical industry and a parallel shift in licensing policy by regulatory authorities to encourage the development of drugs capable of halting 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[237]. What is needed is informed debate on the risks versus potential benefits of this approach.

Where do we ~~think we~~ want to go?

Absolutely key is the recognition that the pathways which initiate asthma and those that propagate established disease are entirely different; early on, cellular inflammation is absent[136], and ICS are ineffective[68,69]. We need to understand the early pathways in detail, so we can develop 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, the last two decades has witnessed the progressive accumulation of data on asthma development from foetal life through to early adulthood (see section 3). While many questions relating to asthma aetiology remain contested, these studies are more remarkable for the broad concordance in many of their findings relating to major asthma-promoting risk factors operative during early life, particularly in regard to the most frequently encountered atopic asthma phenotype. Prominent amongst these risk factors are lower respiratory tract infections and particular patterns of sensitization to aeroallergens, which can act either independently or (more importantly) act in concert to trigger episodic cycles of airways inflammation and accompanying wheezing symptoms[152]. The continued recurrence of these inflammatory events, particularly during the preschool years when postnatal lung growth rates are highest, appears to perturb normal maturation of respiratory functions, thus sowing the seeds for ensuing development of persistent asthma[237]. 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 symptom with persistently low airway function. Allergen i~~i~~mmunotherapy is currently the sole truly disease-modifying treatment at our disposal; whereas the benefits of ICS are lost as soon as they are stopped, the benefit of three annual cycles of grass pollen immunotherapy on allergic rhinitis continued for years after cessation[238].

These findings provide a framework for the systematic testing of a range of therapeutic options relating to primary and secondary prevention, based on the selective targeting of these two interrelated risk factors (lower respiratory tract infections and particular patterns of sensitization to aeroallergens) that contribute significantly to susceptibility to airway symptoms in early life. In principle, inflammation resulting from the local activation of anti-microbial and/or atopic pathways arguably constitutes a plausible acute treatment target in infants and young children with recurrent airway symptoms; however, it is clear that ICS 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 the recent study of year-long treatment of at-risk children with Omalizumab[239] 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 pre further schoolers. Moreover, the successful use of this agent on an autumn/winter-only basis for reduction of exacerbation frequency in asthmatic children[240] provides an illustration of how focusing specifically on known "high risk temporal windows" may also be used to further refine prophylactic treatment protocols. An additional example is the bacterial lysate immunomostimulatordulator OM85, which has been previously been used for attenuation of infection-associated episodic symptoms in adults with COPD[241] and in pre-schoolers with recurrent wheeze[242]: this has recently received regulatory and national funding agency approval in both the US (NCT02148796; https://clinicaltrials.gov/) and Australia (ACTRN12612000518864; www.anzctr.org.au) for use in preventive trials in infants related to later asthma development, and for use in Australia on a "winter treatment only" basis for prevention of exacerbations in school age children (ACTRN12614000062628 ; www.anzctr.org.au).

One difficulty in these and related trials is determining risk – the positive predictive value of many available indices are little better than flipping a coin, although negative prediction is very good[68,243,244]. One problem is thatIt is clear that these predictive indices are based on the crudest markers; a recurring theme is that the respiratory community has by and large failed to rise to the challenge of using modern omics technology to determine predictive biomarkers (also a recurring theme of this Commission), although there has been some progress recently[245]. The first major initiative in this regard targeted prevention of allergic sensitization in high-risk infants by immune tolerance induction employing prophylactic allergen-specific sublingual immunotherapy, aiming to reduce ensuing asthma development by age 5-6 years. This trial was downgraded to pilot status after recruitment of only 50 children, enabling subsequent collection of safety data only[246]. However, it is noteworthy that a conceptually identical trial funded subsequently by the National Institute of Allergy and Infectious Diseases (NIAID) aimed at prevention of allergen-specific sensitization to food allergen by oral administration of tolerogenic doses of allergen has successfully achieved its primary endpoints[247], and a smaller sublingual tolerance induction trial in the UK funded by the Medical Research Council (MRC) targeting prevention of sensitization to aeroallergens has achieved partial success[248]. This approach clearly shows promise and should be systematically followed up. Encouragingly, a number of such studies are in 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[226]. The direct approach of specifically targeting the relevant pathogens is complicated by *inter alia* the broad spectrum of viral and bacterial agents potentially

involved, that parts at least of the microbiome are important for early immune development and must be carefully preserved, the lack of relevant vaccines, and potential dangers of bacterial drug resistance associated with over-use of antibiotics. Attacking the problem via enhancement of the overall efficiency of developmentally compromised host defence mechanisms via the use of microbial-derived agents exemplified by pro-/pre-biotics has been widely discussed but at this stage the effect size of such treatments appears modest[249]. One issue likely related to this is the imprecision with which the contents of specific pro-/pre-biotics is known. Emerging data on the use in high risk infants and children 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 OM85, discussed above. Finally, early but important data on the effect of fish oil supplementation of the diet has, for the first time, provided compelling evidence of a positive effect on the natural history of childhood wheezing illnesses[250].

The single factor limiting progress in this potentially exciting area is the lack of relevant paediatric safety data. In this respect Omalizumab is a prime example. This effective biological treatment has been in use in adults for 15 years, and yet the necessary safety data in children under school age which would open up possibilities for primary prevention trials in high risk pre-schoolers is still not yet available. The range of potent and increasingly selective type-2 cytokine blockers available for adult asthmatics is growing rapidly[3,27-29], along with other relevant drug classes such as those targeting innate immunity[251], but there is little evidence of other than token interest on the part of drug manufacturers or the governmental agencies, which effectively set the drug development agenda, in changing the prevailing paradigms. Might a fast-track scheme be useful for moving some impressive drugs forward in paediatric severe asthma? For this to succeed, it would be important for paediatric investigators to contribute patients, which has been a problem in recent years[252]. ~~The chances of committed researchers leveraging off these emerging advances in therapeutics for prophylactic purposes accordingly remain depressingly remote.~~

We would have to conclude that the chances of committed researchers leveraging off these emerging advances in therapeutics for prophylactic purposes is depressingly remote. In this regard, federal legislation in the US dating to 1998 mandates that FDA play an active role in encouraging the manufacturers of existing and new drugs for the treatment of established asthma, to test the same drugs in early stage disease in childhood[253]. But there is no evidence of this mandate being effective. As many researchers in this area can attest on the basis of personal experience from discussions with industry colleagues, business plans associated with release of new asthma drugs rarely include a

serious paediatric component, and never include *prevention*. This will not change unless the clinical/research/regulatory communities become proactive in arguing this case more forcefully. This is a very crucial but delicate issue. Remission-inducing and curative strategies might require billions of dollars invested in clinical trials. Recent curative medicines have attracted price tags in the $US300000-1 million range. Will industry be ready to kill the 'cash-cow' of long-term palliative medications by funding studies which potentially will obviate their need?

So in summary, no more 'me too medicines' should be developed but real energy should be directed to going from control-based treatment to prevention or cure.

SECTION 5: ATTACKING ASTHMA ATTACKS

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

It is important to be clear about terminology. Definitions vary and some events, such as episodes of increased symptoms and/or increased airflow limitation picked up on review of diary cards, have been identified as 'mild exacerbations' in some studies[81,254]. These episodes tend to be responsive to short acting beta agonists given for relief and are prevented by long-acting beta agonists whereas events leading to prescription of oral corticosteroids or hospital admission are less so[81,176], suggesting important differences in pathogenesis. There is evidence that a key difference is that more severe events (i.e. those resulting in unscheduled medical attention and/or unscheduled use of oral corticosteroids) are associated with loss of bronchodilator responsiveness and the presence of airway inflammation[255]. Events defined in this way have proved to be a robust outcome measure and are highly responsive to anti-inflammatory treatment. However, yet again we need objective biomarkers of different inflammatory patterns associated with deteriorations, and of their recovery, rather than 19th century, subjective approaches.

One consequence of not clearly discriminating loss of symptom control from genuine attacks has been that the inadequate word 'exacerbation' (or 'exasperation' as many patients understand it) has crept into our descriptions of acute asthma attacks. This 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 setting 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 the former have mortality rates and costs comparable to those of heart

attacks[256]. CF lung attacks are associated with more rapid decline in lung function and increased risk of death or lung transplantation[257]. Repeated asthma attacks are also associated with a more rapid decline in lung function: in a post hoc analysis of the START study, in children and adults, but interestingly not adolescents, there was an accelerated decline in spirometry in those experiencing an asthma lung attack while on placebo, but not on budesonide[258]. Importantly, the protective effect of budesonide suggests that 'something CAN be done'. Whether the 'exacerbations' were related to poor adherence or the intrinsic severity of the disease is irrelevant to the question of whether 'lung attack' is a useful term. What is clear is that what has hitherto been called 'exacerbation' is not a temporary inconvenience, but a sign of a worse prognosis, which should call forth immediate action.

An additional problem related to the dissociation between symptoms/disordered airway function and the risk of asthma attacks discussed above is that it cannot be assumed that an asymptomatic patient with normal lung function is free of risk[259]. Current monitoring algorithms and asthma treatment goals will have ~~not changed~~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[260]. The recent UK national enquiry into asthma deaths identified, once again, that apparently low risk patients continue to die of asthma; the tragic absurdity of this concept is discussed below[78]. We need new management algorithms 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 in section 2. For this assessment we need to move beyond the airway, to extra-pulmonary and environmental/lifestyle factors[118]. We need to understand 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~~.~~

Finally, our 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[261,262]. The acute attack provides a unique opportunity to offer a root and branches review of the circumstances of the attack in a captive and potentially more receptive patient. Are we making the most of this opportunity? We know that patients admitted to hospital with an acute attack have a poor prognosis and a high rate of ~~readmission~~requiring additional treatment, particularly in the short term[263]. Could we do more to prevent this happening? A first

step might be an end to the prescription of a fixed term dose of oral corticosteroids with no follow up to assess response. Secondly, treatment protocols should mandate a re-assessment of all aspects of care to identify: (1) what went wrong and could it have been prevented; (2) was the response correct in terms of the treatment plan; and (3) should the treatment plan be altered with the wisdom of hindsight?

There is an even greater problem with 'wheeze attacks' in pre-school children. Here there is conflicting evidence that either corticosteroids[264-266] or leukotriene receptor antagonist therapy[267] reduces the risk of attacks or are useful in the treatment of attacks[196,268]. There is a huge need for effective therapies in this age group.

Where do we ~~think we need~~want to go?

Our limp response to 'exacerbation' is in stark contrast to the Cardiologists' focussed, highly effective and life changing response to a 'Heart attack'. We should emulate them. So:

1. 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. Patients and families need to know this.
2. A lung attack should prompt a full review of all aspects of the problem, including co-morbidities, management, adherence, adverse environmental factors and psychosocial issues, which must not be permitted to decline into a box-ticking exercise.
3. We must make the most of opportunities to prevent these episodes. In many countries there are high risk periods for asthma attacks, including returning to school in the autumn, thunderstorms in early summer and the winter respiratory virus season. Attacks during these periods are particularly inflammation driven~~ory~~ and may therefore be readily preventable with regular or as required ICS[185] or biologics[240]. 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.
4. We must communicate the meaning and consequences of an asthma attack more effectively to our patients and to other stakeholders. The assessment of risk of a recurrent lung attack should be as big~~–~~ a part of the routine management of airway disease as it is in cardiac disease.

We could do more to understand the heterogeneity of asthma attacks at all ages, and the basis of 'wheeze attacks' in pre-school children. We have assumed that viral infection is the inevitable

trigger, but bacteria are frequently isolated[154] (although whether cause or consequence is not easy to determine), and we need to understand if there are subgroups who should be treated with antibiotics without corticosteroids. Studies in patients with COPD lung attacks show that patients presenting in a similar way can have strikingly different patterns of airway inflammation[269]. There is increasing evidence 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[270,271]. Importantly, inflammatory patterns of attacks are repeatable within adult patients and can be predicted from findings when stable[269]. The 'treatable traits' approach to the treatment of stable airways disease discussed in section 2 could therefore be just as applicable in patients presenting during an acute attack, and in planning the best approach to prevention of a recurrence.

One interesting question is whether specific biological treatments have a role in treatment and secondary prevention of attacks, at least in adults. The IL-5 receptor blocker Benralizumab has a rapid and very complete suppressive effect on blood eosinophil count[272] suggesting that it might have utility as an alternative to prednisolone treatment in patients with eosinophilic exacerbations. There is already evidence that treatment reduces the rate of relapse in patients presenting with an attack[273]. The administration of an injected, long-lasting anti-inflammatory agent might have particular advantages in a situation where 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-agonist consumption, a high short-acting beta agonist/ICS 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[260]. Such a review could result in a risk score, similar to cardiovascular risk assessment, and an individualised recommendation for reducing risk. Might such an approach reap the same sorts of benefits currently being enjoyed in cardiovascular medicine?

SECTION 6: GETTING SERIOUS ABOUT SEVERE DISEASE

Where are we ~~stuck~~ now~~, and why is it such a bad place~~?

The national report on asthma deaths (NRAD) stated that 60% of asthma deaths were in patients with 'mild' asthma[78]. This is clearly a nonsense, and our definitions of severe asthma must be wrong, since it is difficult to think of a worse outcome than death! The conventional definition is of symptoms, poor lung function and/or exacerbations (used interchangeably) despite being prescribed high dose anti-inflammatory and bronchodilator therapy[274]. This subset of patients (about 20% of the total) is referred to as having 'difficult to treat' or 'difficult asthma'. In many cases, after detailed systematic evaluation, a co-existent problem is identified (see Table 5 and 6), either alone (misdiagnosis) or together with mild/moderate asthma ('asthma plus'), and when effectively managed, symptoms can be controlled[275]. However, currently although lip service is paid to optimising basic management, in practice often very little is done beyond asking the patient if they are taking treatment. The biggest elephant in the room is adherence, an important factor even in those referred to tertiary level severe asthma centres[276]. A readily available protocol-driven adherence assessment would minimise the risk of committing a patient to long-term expensive biological treatment when their disease is readily controllable with inhaled treatments; one way, modifying medication delivery devices, is discussed above.

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Some patients within this wider difficult asthma group have 'severe asthma', which cannot be controlled with currently available treatments 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 ICS plus a second controller for the previous year or systemic corticosteroids ≥50% of the previous year) to either maintain asthma control or which fails to achieve control (box ~~4~~6)[274]. Severe asthma represents a significant unmet medical need and is the subject of intense mechanistic and therapeutic study, which needs to be brought into the clinic. Novel therapeutics, targeting a particular severe asthma phenotype (severe eosinophilic asthma), have started arriving in the clinic and will substantially increase management options for this group. Precise clinical assessment, with a particular focus on ICS adherence, is critical 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, where there is substantial remaining ignorance and therapeutic need. Ultimately, in all the asthmas, we need pathway defined approaches and treatments.

Where do ~~we think~~ we want to go?

A better definition

Difficult asthma is NOT a diagnosis but is an 'umbrella term' to describe a clinical problem, which requires careful multi-disciplinary assessment. It must be modified to include a component of risk, based not merely on airway phenotype, but also extrapulmonary co-morbidities and social/environmental factors. The first and most important challenge is to find a definition that includes risk assessment and reflects clinical reality. The recent ERS/ATS taskforce document definition[274] (box 6~~5~~) recognised that different criteria can be used to define severe asthma and does not assume that these are pathogenically similar. Our proposals develop~~s~~ this important conceptual shift and focuses more explicitly on the risk of attacks:

- (all ages) one severe asthma attack should be taken as evidence of severe disease, and trigger a detailed evaluation of the disease
- Spirometry persistently below the normal range despite moderate doses of ICS and one other controller
- Persistent variable airflow obstruction despite prescription of a LABA and ICS combination
- (at least in adults) evidence of persistent airway eosinophilia despite the prescription of a moderate dose of ICS; however, symptoms per se, without evidence of airway eosinophilia, airway dysfunction and no history of exacerbations, should not qualify as 'severe' disease.
- Adverse factors in the behavioural/environmental domain: unscheduled visits, failure to attend appointments, poor adherence, smoking, allergenic environment and the three 'D's – Denial, Depression, Disorganisation.

Clearly a definition on its own achieves nothing; what this definition should achieve is a detailed and focussed response, assessing all aspects of the patient's airway disease, and the treatment plan, rather than assuming that an asthma attack is a mere minor inconvenience. Another need is a detailed and agreed assessment plan. After such an assessment, it may be clear that with good basic management the disease is no longer severe and risk has greatly reduced. However, ~~short term~~short-term amendment may be followed by prolonged recidivism, and ongoing efforts to support better management are essential.

Tackling poor treatment adherence

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The challenge of non-adherence to maintenance treatment exists in all chronic diseases and is also prevalent in difficult asthma. Here again, we have been slow to embrace modern technologies to assess adherence. Obtaining an electronic prescription record is easy but is not always done; if no prescriptions are being collected, then no medication is being taken. The next step, used in some centres, is the use of a micro-chip to monitor when the device is being activated[277]. But this does not

say that the patient is actually inhaling the drug correctly. It is not difficult to say that we need a device which 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 (say) three doses are omitted or rolling cumulative adherence drops below 80%, or, in the case of SABA, more than a set number of doses are taken in a particular time frame. We should mandate that all inhaled medications must be dispensed in such a device and so should healthcare payers. Naïve? We would ask ~~that the power of the modern smartphone is compared to those in the old fashioned coin operated telephone booth, and then ask~~ why during ~~this~~ our current technological revolution, inhaler monitoring technology has stalled, or rather, never got started in the routine clinic (see section 2).

Recent 'biomarker based' assessments of corticosteroid response may identify patients who should achieve good asthma control with better adherence to standard treatment and without escalation to some of the novel expensive parenteral biologic therapies[278]. Assessments of this kind must replace a 'suck it and see' approach to this needy 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

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A number of comorbidities are commonly reported in a population with severe asthma (Tables 5,6) and management guidelines advocate identification and management of these conditions. However, the evidence that managing these comorbidities has a major clinical impact on asthma outcome in this population is limited. For example, despite a substantial literature discussing the relationship 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[279]. This may be because non-acid reflux is still occurring or because the presence of gastro-oesophageal reflux has little impact on underlying asthma but triggers cough perceived as asthma, either because asthma causes reflux, β_2-agonists increases reflux, or reflux is a harmless fellow-traveller. Gastro-oesophageal reflux can be effectively surgically treated with fundoplication and efficacy has been suggested in asthma[280]. However, a "sham controlled" fundoplication study has never been performed although this type of study is feasible and has been useful in assessing established surgical practice in other disease areas.

Similarly with obesity, the precise link with severe asthma remains unclear; however, discrete obese phenotypes have ~~consistently~~ emerged consistently in cluster analyses of severe asthma

cohorts[23,281]. 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[115]. However, the benefits of weight-loss reduction programmes and bariatric surgery, whilst encouraging, remain unclear[282,283]. As can be seen from these examples, a challenge for the future will be to tease out association from "cause and effect" for all of the commonly reported morbidities in severe asthma, which will allow better targeting of interventions, including invasive surgical procedures, in this patient group.

Precision, biomarker directed medicine in severe asthma

Recent data in adult patients with severe asthma, suggests there is evidence of more significant heterogeneity of airway inflammation. 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[10,23]. In severe asthma patients with no evidence of type-2 inflammation, it is likely that their corticosteroid dose has been escalated inappropriately to try and manage persistent symptoms which are not corticosteroid responsive[10]. Given the evidence that corticosteroid responsiveness is confined to type-2 high disease[6,284], 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. Adjusting corticosteroid treatment using sputum eosinophil count has demonstrated benefit in terms of exacerbation reduction at least in adults[10,11], but repeated sputum analysis has been challenging to deliver in routine clinical care, and the results are variable in children[285]. Moving away from the currently advocated symptom driven escalation of corticosteroid treatment, particularly in patients with severe asthma, will be a major component of delivering 'precision treatment' in severe asthma in the future and facilitate optimisation of corticosteroid dose. It would also allow a diagnosis of severe asthma to be made without escalation of corticosteroid treatment past a point where in many cases, there is unlikely to be any therapeutic benefit.

Some patients with type-2 high disease have refractory eosinophilic asthma, where despite adherence with high dose inhaled corticosteroids, there is persistent type-2 cytokine driven inflammation and airway eosinophilia. Currently, these patients (comprising around 3% of the total asthma population) frequently require regular or frequent courses of systemic corticosteroids to improve disease control. They develop well-recognised side-effects including osteoporosis, diabetes,

hypertension, cataracts, psychological disturbance, Cushingoid features, ~~-~~and airway and systemic infections[286,287]. 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 ~~is~~ has been ~~currently~~ available in the clinic for some time. Clinical trials have demonstrated reduced unscheduled emergency visits and hospital admissions[288], and current guidelines advocate the use of Omalizumab as an add-on therapy in severe asthma[274]. However, it is problematic that serum IgE is not a useful biomarker of treatment response[289] and that there remains a reliance on non-specific clinical measures of asthma severity to guide prescription decisions[289]. The risks and benefits of biologics must be assessed objectively by biomarkers that are demonstrably and plausibly linked to the targeted biological process (i.e. FeNO for Omalizumab[289]). Otherwise, there will be an unacceptable and inefficient reliance on treatment trials in individual patients.

~~Many n~~New biologic therapies targeting IL-5 are now available for use and other biological agents targeting type 2-high disease will potentially be available in the next 5 years (table 2). This~~ and~~ will generate many interesting questions, including differential efficacy between monoclonal antibodies targeting IL-5 (Mepolizumab and Reslizumab), the IL-5 receptor (Benralizumab), IL-13 (Lebrikizumab, Tralokinumab) and IL-4Rα (Dupilumab). Other strategies ~~targeting~~ inhibiting the type-2 axis including orally active CRTH2 antagonists (Fevipiprant)[290] and anti-TSLP[291] will also be targeting overlapping patient groups. Identifying which patients respond better to different classes of drugs may require 'head-to-head' studies, which are unlikely to be funded by Pharma. Many of these new therapies will come to market with a companion diagnostic or predictive biomarker of clinical response. Before release, it is essential that clinical trial data are made 'open access' and individual patient biomarker data analysed independently with the aim of identifying biomarker signatures predictive of efficacy of treatment. Patient organisations and healthcare payers should lobby pharma to ensure this happens.

There is already evidence that different biomarkers identify different aspects of type-2 mediated inflammation (tables 1 & 3). Both an elevated blood eosinophilia or FeNO is associated with the risk of severe asthma attacks but a greater risk is evident if both are elevated [100]~~For example, a blood eosinophilia is more closely associated with the risk of severe asthma attacks than a raised FeNO~~[100]. Existing data ~~also~~ shows differences in the ability of biomarkers to predict treatment responsiveness.

FeNO and serum periostin are good biomarkers of treatment response to biological agents inhibiting IL-13 in adults with severe asthma[29] whereas the blood eosinophil count is most closely associated with a response to anti-IL-5[12] (table 3~~2~~). Moreover, treatment with anti-IL-5 reduces the blood eosinophil count but not FeNO[12] whereas the reverse is true for anti-IL-13[29]. It is therefore possible that biomarkers profiles can be used to identify sub-groups of patients within the type-2 high population who have different risks of attacks and are particularly suited to different cytokine blockade. Whether post-hoc analysis of existing research databases is sufficient to tease such out these relationships is uncertain. Prospective information will be important and we suggest that biologics should: (a) only be prescribed in tertiary centres after a protocol driven assessment of why the patient is not responding to standard therapy; (b) should be subjected to a protocol driven therapeutic trial, with collection of clinical and preferably biological data in a standardised manner; (c) this information is collated and made available via a publically available database; and (d) more information is needed on treatment of severe childhood asthma.

All biological agents targeting type-2 cytokines have a larger impact on the risk of future attacks than on ongoing symptoms and lung function impairment (table 3). They are also likely to be expensive so health care payers will be keen for treatment efficacy decisions to be made early. This presents challenges as short-term changes in symptoms 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. It is also possible that this approach is not valid because the mechanism of short-term ~~symptom~~ 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 based on 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 radio frequency energy to the airways with the aim of reducing airway smooth muscle mass and hyperresponsiveness. The role of thermoplasty in the management of severe asthma remains to be established. What is missing from existing clinical trial data is good evidence that response is linked to a particular pathophysiological abnormality, or trait (table 4)[292,293]. Thermoplasty treatment is thought to reduce airway responsiveness via a direct inhibitory effect on airway smooth muscle responsiveness, but such an effect has not been demonstrated 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[294], 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.

It is already clear that asthma symptoms and altered physiology often manifest in the absence of type-2 inflammation but we have limited information on what 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[139]. In addition, recent research has highlighted the association between systemic inflammation, especially systemic IL-6 inflammation and outcomes of severe asthma and raised the possibility that inflammatory mechanisms that arise outside the lung may cause lung injury[115]. These mechanism may relate to the inflammation that occurs with ageing and increasing body weight. Such mechanisms include inflammation associated with metabolic dysfunction including IL-6 pathways and pathways related to insulin resistance[115]. Importantly, some of these pathways are tractable in terms of treatment.

The greatest future challenge in severe asthma remains ‘disease modifying’ therapy and cure. It is attractive to speculate that if we could understand why patients with a pattern of disease (type-2 high), which is usually responsive to low doses of inhaled corticosteroids, becomes ‘relatively’ corticosteroid resistant and requires high dose (often systemic) treatment, we could target this therapeutically. This area has been the subject of study for many years, but no precise mechanism, as evidenced by a proven therapeutic, has as yet emerged.

SECTION 7. IMPROVING RESEARCH

Clinical trials

Over recent decades, clinical research has been characterised by randomised controlled trials (RCT) of moderate and severe asthma, in populations poorly generalizable to asthma patients in clinical practice[166], without characterisation of phenotypic subgroups, and inadequate consideration of other treatable traits related to overlapping disorders, comorbidities and lifestyle or environmental factors. It could also be argued that progress has 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 of 'me too' trials of ICS/LABA medications. The focus on moderate and severe asthma in trials based primarily in tertiary hospital research institutions, has meant that there is a limited evidence base 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 the greater utilisation of primary care based research centres. However, the onus will then be on the primary care centres to improve diagnosis and monitoring of airway disease in their patients, and (not just in primary care) ensure that patients actually have an airway disease the nature of which is known, and are taking conventional medications appropriately before 'something new' is trialled. There is huge untapped potential for asthma research in primary care, which utilises electronic medical records containing clinical, laboratory and health utilisation outcome data. It is encouraging that this opportunity is being exploited so effectively in the Salford Lung Study[295] and by the Research Effectiveness Group[296].

Research also needs to encompass the spectrum of ages in which asthma occurs, including pre-school and school age children, in whom there is a paucity of clinical trials, yet paradoxically high burden of disease. For similar reasons, resourcing also needs to be provided to ensure more RCTS are undertaken in low and middle-income countries, as well as high income countries, and that medications are affordably priced for LMICs. The European Asthma Research and Innovation partnership have recently published an excellent report[297] emphasising the need for a joined up approach to future research in asthma and highlighting areas of particular need. This work provides a solid framework for improving the quality of research and, ultimately, asthma outcomes.

The issue of the external validity of evidence from RCTs is crucial in determining whether the findings inform the likely benefits and risks of a proposed treatment to individual patients. The traditional requirements of major RCTs to mandate that participants have marked bronchodilator reversibility, limited smoking histories, and designated symptom, reliever use or lung function parameters has 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 RCTs which have informed guidelines, on which recommendations for their management have been made[166]. Of course this may in part be because the asthma label is incorrect. The requirement for bronchodilator reversibility for participation in clinical trials has meant that the benefits of long-acting bronchodilators may have been over-estimated. Our failure to require evidence of active

eosinophilic airway inflammation means that the benefits of ICS and other more specific inhibitors of this process may have been diluted and thus underestimated.

The Commissioners believe that features such as bronchodilator responsiveness, severity of asthma, diagnostic label, level of control, health care utilisation and smoking history should not be inclusion/exclusion criteria, but rather key covariates and potential predictors of response with the study powered for sub-group analysis. These would supplement the use of biomarkers of type-2 disease, which already have established utility as predictors of response to ICS and monoclonal antibody therapy directed against associated cytokines. In this way the findings from RCTs will not only be more generalizable to patients with asthma managed in clinical practice, but will also enable identification of sub-groups having a preferential beneficial, or a higher risk of adverse responses. Initial RCTs of broad populations could be followed by RCTs undertaken in highly characterised groups whose response to intervention is different in a clinically important way. Focused RCTs would also be applicable early on when the treatment target and its relationship to disease expression are well known. This approach will ensure that the findings have high external validity to such specific phenotypic groups. It would help rather than hinder the development of the precision approach to management outlined in sections 1 and 2. Table 4 provides information on the target population, potential covariates and most rational outcome measures for established treatable traits.

There is a growing awareness that while standard outcome variables such as lung function, composite measures of asthma control and health care utilisation provide a multidimensional assessment of efficacy and risk, they may be inadequate alone if a comprehensive assessment of efficacy and safety is to be obtained. This is illustrated in the differing, and at times heated, debate over the interpretation of the large RCTs of the single ICS/LABA maintenance and reliever therapy regimen, in which the lack of objective measures of medication usage contributed to the difficulty in assessing key outcomes such as beta agonist overuse, delay in seeking medical help during asthma attacks and systemic corticosteroid exposure[298]. A highly rigorous, RCT in high risk asthma subsequently showed the potential of electronic monitoring of medication use to objectively measure such clinical features of a therapeutic regimen[246]. This study not only demonstrated the favourable efficacy and safety profile of this single ICS/LABA maintenance and reliever therapy regimen in high risk asthma, but also set a new benchmark for RCTs in which patterns of medication use are electronically recorded.

There is also growing awareness of the need to place a greater emphasis on the investigation of the treatment of overlapping disorders, comorbidities, 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 may not only improve outcomes, but also move the field towards precision medicine in asthma.

Integrating epidemiology, genetics and translational research

A huge number of observational, cross-sectional and longitudinal studies have been performed lacking detailed clinical descriptions of affected patients; the basic science has been spectacular, the clinical characterisation limited. One of the main challenges to understanding the epidemiology and genetics of asthma is the lack of consensus in defining the disease, which is in part a consequence of the underlying heterogeneity (see section 1). Unless epidemiologic and genetic studies find better ways to distinguish between different diseases under the umbrella diagnosis of ~~"~~asthma~~"~~ at a population level, it will be impossible to discover their unique underlying genetic risk factors, or identify novel therapeutic targets for stratified treatment, as any signal will be diluted by phenotypic heterogeneity[299]. This heterogeneity may result in discrepancies between different studies estimating asthma prevalence and associated risk factors. As an example, a recent review has demonstrated that in 122 epidemiological publications investigating risk factors for childhood asthma, no fewer than 60 different definitions of "asthma" were used[300]. However, it is of note that applying four most commonly used ~~"~~asthma~~"~~ ~~of~~ criteria to a high-risk population of children resulted in the overall agreement of only 61%, suggesting that 39% of study participant may move from being considered "asthma cases" to "non-asthmatic controls", purely depending on which definition was used[300]. The overall impact 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 characterized subjects affected by wheeze, cough and asthma as in clinical settings by measuring in detail the traits we discuss in section 1 and in table 4. Fear of and malaise in cross-disciplinary collaborations between epidemiologists, clinicians, geneticists, immunologists and numerous other specialties has built up borders and fences and encapsulated visions.

Given the functional interdependencies between the molecular components in a human cell, mechanical characteristics of the lung, asthma is rarely a consequence of an abnormality in a single gene, a single environmental factor nor a single functional abnormality of the lung. Asthma reflects more 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 mechanism of a particular disease, leading to the identification of disease modules and pathways, but also the molecular relationships among apparently distinct endo- or phenotypes[301].

While the complexity of the scientific world is ever increasing and specialties are struggling to keep up with the exponential rise of information and data, we have neglected to reflect about overarching general concepts of disease inception. Epidemiological attempts to isolate a few determinants out of a sea of confounding factors do not live up to a complex asthma syndrome, as discussed in section 3. We will not identify the magic bullet that will solve the asthma epidemic across the world. There is also very little appreciation that different biological pathways flow in clinical features termed 'asthma' which are not necessarily reproducible in other environmental and ethnic contexts. Striking examples are found in genetic studies where different genes for asthma are found in different ethnic groups[302].

Genetic research has addressed the hereditary component of asthma (usually defined as parentally or patient-reported "doctor-diagnosed asthma") in a number of large genome wide association studies (GWAS). While heritability estimates suggest that about half of the risk variation is attributable to genetic factors[303], GWAS have identified only a few common variants accounting for only a small part of asthma risk[304]. 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 GWAS accounted for only 38% of childhood onset asthma cases[304]. In addition to the GWAS initiatives, a wide array of candidate genes, all with weak effects, have been identified[305]. Of note, when a much more precise and specific definition was used (early-life onset asthma with recurrent, severe exacerbations in pre-school age), GWAS has identified associations with a much greater effect size, and novel susceptibility genes such as *CDHR3* (cadherin-related family member 3, rs6967330, $C_{529}Y$]).[306] Subsequent studies have shown that CDHR3 expression facilitates rhinovirus-C binding and replication, and that a genetic variant which was linked with hospitalizations for early-onset childhood asthma in birth cohort studies mediates enhanced RV-C binding and replication[307], providing further indirect evidence that we need to move away from using problematic umbrella terms in epidemiology and genetic studies. This sort of triangulated approach will be really important in future genetic and epidemiological studies.

Similarly, most of the known environmental risk factors for asthma also have weak effects[308], as discussed above. 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 relationships remains unclear. One of the most replicated examples of gene-environment interactions to date is that between endotoxin exposure and variants in *CD14* gene. Several studies have confirmed that high endotoxin exposure is protective against allergic sensitization, but only among individuals with a specific genotype (C allele homozygotes of *CD14/-159,* rs2569190), and not in those with other genetic variants[309,310]. A further complexity is added by the interactions with other environmental exposures (e.g. dust mite exposure), resulting in a complex gene by environment interactions[309]. Further examples include the observation that the same environmental exposure may have opposite effect on asthma among individuals with different genetic predisposition (for example, the effect of early-life day care attendance on asthma development goes in the opposite direction in children with different variants in the *TLR2* gene, with day care being protective in some, but increasing the risk in others)[311]. The lessons for intervention studies (including primary prevention) is that when identifying environmental protective/susceptibility factors which are amenable to intervention, individual genetic predisposition will have to be taken into account to enable the development of personalized strategies[312]. Thus, not only the treatment, but also prevention will have to be stratified.

Another often neglected issue is that the effects which are often attributed to environmental exposures may actually be a reflection of genetic predisposition (gene-environment correlation). Recent examples include the finding that the association between antibiotic use and childhood asthma (which is often attributed to antibiotics changing the host microbiome), may arise as a result of confounding, in which impaired antiviral immunity/increased susceptibility to virus infections increases the likelihood of both early-life antibiotic prescription and later asthma, with both asthma and early-life antibiotic prescription being associated with the same genetic variants on 17q21[313].

The translation 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 requirement for interventions to be easily introduced and taken up at the community level would enhance both participation in the research and its

subsequent implementation if proven effective. This requirement is illustrated by the dilemma of the studies of multifaceted allergen avoidance/dietary/tobacco smoke avoidance strategies[314], 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 from high zone tolerance to the sensitization range. This concern, together with the expensive and burdensome nature of the interventions has limited 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 SABA for episodes of wheezing in infancy and whether it may increase the risk of established asthma in childhood. This hypothesis is based on the demonstration that inhaled SABA therapy increases airway hyperresponsiveness in both children and adults[315,316] and can do so within weeks. However, there would be major practical barriers encountered with attempts to undertake such a study, or change practice as a result of such a study, as any restriction in beta agonist use contradicts current dogma in terms of the treatment of ~~asthma~~ wheeze in infancy.

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

We may require an innovative combination of trial design and statistical methods to overcome the main limitations associated with conventional RCTs. Such an innovative approach would be a randomised platform trial which uses Bayesian statistical methods, a priori 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[317]. Relevant subgroups could be identified, a priori, 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 may identify a beneficial effect early in the course of the disease would be an advantage. While 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 RCT. It also enables the study of additional novel interventions which are identified during the course of the study, which is important when the likely 10+ year duration of such studies is considered.

Animal models/basic immunology

Although we have made progress it has been incremental rather than paradigm shifting and we still lack adequate models in key areas. Current animal models do not adequately reflect the distinct clinical phenotypes and endotypes of human disease described above. Currently, the vast majority of models use mice and focus on Th2 phenotypes with high eosinophilia and a type-2 cytokine profile. There are no models that clinically cross-validate models of non-type-2 phenotypes. For example, there are no models that represent neutrophilic asthma, or those that adequately reflect steroid resistant phenotypes. The biology of neutrophilia is, however, very well understood- particularly in pulmonary infection models but translational studies are limited. Models of other clinically important phenotypes are also poorly addressed. There is almost exclusive emphasis on the acute phase of the host response to aeroallergens, and although there needs to be more focus on how to promote resolution of injury very few chronic exposure models exist. Genetic models of chronicity need to be cross-validated against human endotypes.

There is an excessive focus on the mouse as an experimental species, even though pathology in mouse and humans varies considerably[318]. "Mouse asthma" in most models is a disease of the peripheral lung as opposed to conducting airways. In addition, there is a failure to address genetic diversity issues - almost all 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 due to 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, as well as during different states of development. With the advent of CRISPR/Cas9 technology genome engineering has progressed to the point where it is possible to edit genes to reflect even subtle mutations and investigation into the function effects of SNPs identified in patient populations can take place. In contrast, genetic technologies have not been advanced in rat models, e.g Brown Norway Rats, which have previously been used to model allergic inflammation in vivo. Primate models, e.g., Ascaris sensitivity in Cynomolgus or rhesus monkeys are prohibitively resource

intensive and ethically unacceptable in some countries; but should they be used more as a step between rodent and human studies? Sheep and horse models of asthma have also been described but their widespread use is limited by lack of resources as well as reagents for analysis. Excellent data exists on comparative mouse lung functional physiology but it is not widely understood, thus impeding progress on understanding the functional basis of episodic airflow limitation.

We lack models that adequately address the interaction between viral (and bacterial and fungal) infections in asthma pathogenesis. This incorporates exacerbation models but in particular the clinical reality, which is concomitant challenge with virus/allergen. Generally, those that try and address the issue of exacerbation models focus on viruses[319]. There are beginnings of "relevant" respiratory infection models for mouse, including human rhinovirus (HRV), which is overwhelmingly the most applicable to humans, but the mouse HRV model is not really a good fit for human[320]. Most importantly, we have nothing yet to model the HRV-C subtype, which is the main pathogen in man in relation to asthma. Additionally, it is becoming increasingly evident that particularly during the initiation phase of asthma pathogenesis, bacterial pathogens play a central role as independent risk factors[321], and likely also via interaction with viral pathogens, but there is a dearth of relevant experimental models to probe underlying mechanisms.

Generally, the community is still focusing exclusively on specific pathogen free (SPF) mice, a fact that fails to take into account the microbiome perspective. This is completely at odds with the human situation in which the full spectrum of "hygiene hypothesis" related phenomena are relevant. For example, we know that Treg function is completely different between SPF and microbiologically "conventional" mice[322]. Moreover, microbial status during infancy determines maturation kinetics of both innate/adaptive immune functions and influences subsequent development of allergic responses[323].

There is a large-scale emphasis on immunologically competent adult animals whereas the main human caseload is in early paediatrics – a vital difference, considering that the immune system matures postnatally. We know from human epidemiology that fundamental changes occur in lung and airway growth pre- and postnatally as a result of immunoinflammatory episodes in the respiratory tract during pregnancy and infancy (see above). This obviously helps to set "trajectory" of lung/airway growth/differentiation, which influences development of lung function, but very few studies address this issue.

Translational biology (i.e. mouse and human "omics", GWAS, expression profiling) has not been systematically exploited. Technology to "humanise" mouse models is seldom utilized. The mouse is extremely well understood for drug kinetic analysis but this knowledge is seldom 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 aetiology and pathogenesis. Specific examples include:

- why is it that only ~25% of sensitised/exposed children show clinically significant airways symptoms whereas 100% of sensitised/challenged mice respond?
- why is it that >90% of hospitalisations amongst school children for severe asthma exacerbations are in the midst of an acute virus infection, and of these >80% (probably more) are sensitised to indoor allergens ?
- why are most asthmatics under age 10 years boys? Yet most of the ongoing animal work is performed using female mice.

We need to establish an integrated platform whereby animal models form part of a framework that include 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[324]. We should not be afraid to embrace human in vivo models to answer particular questions that might shed light on molecular mechanisms underlying disease pathways[325,326].

~~CONCLUSIONS~~RECOMMENDATIONS

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~~Perhaps ambitiously, we propose a revolution in thinking about asthma, generalizable to all airway diseases, which, alongside the undoubted importance of optimal delivery of the best care to each patient, will deliver real precision asthma medicines, dissecting airways disease into its components 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 divert us away from a diagnostic and therapeutic *cul de sac* and result in a new system that will be valuable in epidemiological and interventional studies and make it more likely that we unpick pathophysiology and, eventually, develop better medicines and achieve better outcomes for our patients. We hope it will add momentum to the recent encouraging progress in new drug discovery and, as did the first asthma guidelines 25 27 years ago, lead to a decade or more of improved outcomes.~~

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

1. Evolve from 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[327], to use asthma solely as a descriptive label for a constellation of symptoms (i.e. more akin to arthritis than CF). Pathological b~~B~~reathlessness 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 at all. 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 ~~are the components of the~~ 'asthma' (better, 'airway disease') this patient has and how should ~~the~~it~~y~~ be treated? The logical consequence is that, as far as is possible, each patient's airway disease is deconstructed into its component parts before planning treatment, and also focussing in particular on components that are treatable and are reassessed ~~–~~periodically for further treatment adjustment[118]. This general approach is equally applicable in patients with COPD and removes entirely the need to consider overlap categories such as ACOS.

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We have identified traits that have the merits of being measureable, modifiable and linked to morbidity. We acknowledge that this is the start of the process and that better more well-defined traits may 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 where the two dominant identifiable and treatable traits (risk of attacks related to eosinophilic airway inflammation and symptoms as a result of airflow limitation) are assessed and managed, resulting in a more individualised and precision approach. This precision medicine approach is supplemented by broad consideration of treatable traits encompassing overlapping disorders, comorbidities, lifestyle and environmental factors. The simplicity of the approach, and the fact that it could be operationalised across different healthcare systems, makes it an attractive alternative to current guidelines. It has the additional merit of identifying the important gaps requiring 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[163] but this will need to be tested formally in appropriate healthcare settings. Assessment and treatment costs and measures of treatment efficacy are therefore logical outcome measures to use to assess the efficacy of this new approach and, since the use of ICS (particularly at high doses) will be impacted most obviously by the management approach, we suggest that an achievable goal would be to reduce ~~overall~~ high dose ICS consumption by 30% with no overall loss of symptom control and better control of attacks (see below).

2. Move beyond a disease control-based ambition for asthma treatment. We do not need more 'me-too' steroids and LABAs. Resources should be directed toward asthma prevention and cure. We want disease modifying studies, e.g. immunotherapy, early use of monoclonals, which involves finding biomarkers for risk in children, and a better understanding of initiation pathways for airway disease. And we want to provide older patients with hope that their chronic asthma may be cured. Some encouraging initial progress has been made in this area[250]. Our goal is for at least one primary prevention strategy for high risk children and one disease modifying intervention to be identified.

3. Break out of our age- and discipline-related silos and see airway disease in the context of the developmental track from birth to old age. Regulators should be asked to enforce existing guidelines for mandatory~~-~~ testing plans for children as part of ~~licensure~~ licensing process for new asthma drugs. And exploration of the benefits of intervening in utero to prevent asthma can be done, as the recent vitamin D studies and *Bordetella pertussis* vaccine studies have shown [328].

Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network may still be difficult to predict. For future research it is important that the correct principles and concepts are used. A reductionist approach is needed to identify involved mechanism and treatable traits, whereas systems biology need to be implemented in order to address the complexity of the interaction between different components and aging. ~~It is important that~~Our goal is that the reductionist and system based approach are~~are~~ used as complementary, and that the right method is used for the right question.

4. *Test before treat*: We cannot implement precision diagnosis and management or make progress with prevention in children without moving away from the current 'no test' culture in clinical practice. Objective measures of key components of asthma are necessary, including measures of

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lung function in young children, measures of airway immune function, and measures of systemic and airway eosinophilia or neutrophilia[329].

~~Even if all tractable mechanisms in a complex disease are fully understood, the overall functioning of the complex disease network may still be difficult to predict. For future research it is important that the correct principles and concepts are used. A reductionist approach is needed to identify involved mechanism and treatable traits, whereas systems biology need to be implemented in order to address the complexity of the interaction between different components and aging. It is important that the reductionist and system based approach are used complementary, and that the right method is used for the right question.~~

If, as discussed above, about a 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 old, early detection of this high risk group is relevant. First, to reinforce smoking cessation advice in parents and children[330], to implement regular follow-up of lung function and to start treatment as ~~earlier~~ early as possible if needed in order to avoid or delay disease progression. Second, because if lung development has been suboptimal, it is conceivable that other organs might have also suffered similar developmental abnormalities[235]. If this was the case, the early identification of low lung function by spirometry in early adulthood may have public health consequences that reach well beyond respiratory diseases[235]. Spirometry is cheap and straightforward and there are probably several good opportunities 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. Aligning testing to a highly focused and effective educational campaign on the dangers of smoking might have a bigger impact 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 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 affect this change. We hope that changing the name may startle us out of thinking in the rut and change our limp response to these sentinel events to something nearer the cardiologists' focussed, highly effective and life changing response to a 'Heart attack'. We should look again at our current 'one size fits all' approach to treatment and secondary prevention of attacks. Might a more precision approach offer more? Is there a role for biological agents? We will push research in these important

areas across the spectrum of acute wheezing illnesses as the impact on health care systems and patient outcomes could be large.

In terms of prevention, we anticipate that measuring biomarkers will help identify at risk patients and perhaps help them make a decision to commit to life-long prophylactic treatment. We see value in the development of a risk score[260], which could be incorporated into an annual review, and might help to move us from secondary prevention to primary prevention of attacks. The Commissioners will drive the development and validation of this. We have considered difficulties related to 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. Consideration will need to be given to replacing as required SABA with ICS/fast-acting β_2-agonists as reliever therapy~~–~~ in patients with episodic symptoms, depending on the results of ongoing RCT's. This regimen has the potential to have a big impact on the occurrence of severe unexpected attacks[9]. Overall, we see this area as one where very significant progress is possible and consider a realistic goal to be to reduce attack frequency hospitalisation, and mortality by 50%~~ over the next 25 years~~.

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 impact as heterogeneity of clinical and biological aspects is more obvious in severe airways disease[23]. The biological era of treatments will start at about the same time as this commission in published. We must be sure that we use these agents effectively in individual carefully characterised patients. Basic aspects of management must be mastered before going down this path. 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 in having simple and reliable biomarkers of response to biological treatments in school-aged children and adults ~~but not yet~~and potentially in pre-schoolers[329]. We will need to move from a traditional disease category/symptom/lung function based assessment of treatment need and response to one where decisions are driven by the presence and responsiveness of the

relevant trait. We must make progress in the 'which biological for which patient' sphere by collating phase 2 and 3 clinical trial data and carefully collected post-registration patient data with the goal of identifying responsive sub-groups. Trial data must be made available for individual patient data analysis. This is another area where very significant progress is possible. A realistic and very important goal from the patients' perspective is to reduce by 50% exposure to regular and rescue oral corticosteroids ~~over the next decade~~.

7. Better research. The commissioners will work in collaboration with ~~pharma~~ Pharma to ensure that future clinical trials establish not only treatment efficacy and safety but identify definable sub-groups 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 measure to those associated with 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 lunacy of trialling bronchodilators in patients selected on the basis of the presence or absence of a bronchodilator response at baseline, and evaluating drugs targeting eosinophilic airway inflammation in patients who don't have this characteristic.

We suspect that these changes will be readily understood and accepted by regulatory authorities such as the FDA as their primary concern is that trials are carried out in well-defined populations. Currently this means populations that ~~–~~have the diagnostic characteristics of the condition (i.e. 'asthma' or 'COPD') set out by relevant guidelines. When the guidelines change, so will the authorities. However, we must ensure that they are aligned to any proposed change. Our goal is for clinical trials of the future to focus of 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 'test before you treat', we insist on 'test before you research' – what airway disease is actually being studied? ~~We should~~Our goal is to 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[331]. Animal models need to be closer to real life, including pregnancy exposures, viruses and allergens, rather than just single

factors. Despite the cost of large animal models, these represent an important stage between mice and men. Using a range of ~~These sorts of~~ animal models offer us the best prospect for unpicking the complex interplay between different inflammatory pathways, defining why aberrant inflammatory pathways perpetuate and identifying preventive strategies.

The time traveller from the days of Harry Morrow-Brown and the earliest use of cellular markers to guide treatment[2] would find that, while technology and molecular biology have progressed hugely, in airway disease very little has changed at all. What will a time traveller from today find in ~~20~~ 25 years' time? It is the hope of the Commissioners that this will be objective, biomarker driven analysis of airway diseases across the age spectrum, rather than facile umbrellas; 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 on the basis of real-time data transmitted to patients and physicians, with consultations using modern communication methods; and those at high risk in the up and coming generation (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 to spin out into research, whereby the geographical diversity of airway diseases is appreciated not ignored; that the sophistication of scientific studies will be matched by appropriate clinical assessment of the disease; and that animal models will truly reflect human disease. This Commission represents a chance to start this process; and if it is ignored, the time traveller from the 1950's will still find us stuck in the rut in the 2050's.

CONTRIBUTORS

IDP and AB coordinated the data gathering and organised the Commission meetings and teleconferences. The report was drafted by IDP, RB and AB. All commissioners contributed to the report concepts, recommendations, writing, and editing. under the direction of the co-chairs and a supporting research team.

CONFLICTS OF INTEREST

IDP reports grants from GSK, Afferent and Atopix; honoraria and speaker fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GSK, Almirall, Dey Pharma, MSD, Schering-Plough, Novartis, Napp, Regeneron, Teva, Knopp, Chiesi and RespiVert. RB reports personal fees from Health Research Council of NZ, GlaxoSmithKline, AstraZeneca, Novartis and grants from AstraZeneca, Chiesi, Cephalon, Genentech, GSK, Novartis, Sanofi Aventis. AA reports grants and personal fees from Astra-Zeneca, GSK, MSD, Menarini, Novartis and personal fees from TEVA and

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Chiesi. GPA serves on advisory boards for Novartis, GlaxoSmithKline, AstraZeneca, Pieris Pharmaceuticals and Boehringer Ingelheim. EB reports personal fees from Sanofi, Novartis, AZ, TEVA, GSK, Vectura, Boehringer, and grants for research from GSK, AstraZeneca, Roche, Novartis. GB has received fees for lectures and advisory boards from Astra Zeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva and Zambon. PC has nothing to disclose. AC reports personal fees from Novartis, Regeneron / Sanofi, ALK, Bayer, ThermoFisher, GlaxoSmithKline, Boehringer Ingelheim. FMD has nothing to disclose. JF reports grants from Pfizer, Genentech and Vitaeris; he is named inventor on a patent describing biomarkers of Th2 high asthma and on a patent describing thiol modified carbohydrate compounds as novel mucolytic drugs (no income). UF has nothing to declare. PG reports grants from NHMRC Australia and personal fees from AstraZeneca, GlaxoSmithKline, Novartis. LGH reports grant funding from MedImmune, Novartis UK, Hoffmann-La Roche/Genentech Inc., AstraZeneca and GlaxoSmithKline; has taken part in advisory boards and given lectures 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 (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim and GlaxoSmithKline); and has taken part in asthma clinical trials (GlaxoSmithKline, Schering-Plough, Synairgen and Hoffmann-La Roche/Genentech), for which his institution was remunerated. He is also Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with Amgen, Genentech/Hoffman-La Roche, AstraZeneca, Medimmune, Aerocrine and Vitalograph. PGH has nothing to disclose. MH reports personal fees from Astrazeneca, grants and personal fees from GSK, personal fees from Novartis, personal fees from Roche, Sanofi and TEVA. CL has nothing to disclose. GM reports grants from AstraZeneca, grants from GlaxoSmithKline, Novartis Pharmaceutical and the International Union Against Tuberculosis and Lung Disease. FDM reports grants from NIH/NHLBI, NIH/NIEHS, NIH/NIAID, NIH/OFFICE OF THE DIRECTOR, and Johnson&Johnson, personal fees from Consultancy to Copeval and Commense. PDS has nothing to disclose. EvM reports personal fees from PharmaVentures, OM Pharma, Decision Resources, Novartis Pharma SAS, The Chinese University of Hongkong, University of Copenhagen, HAL Allergie GmbH, Ökosoziales Forum Oberösterreich, Mundipharma, American Thoracic Society, AbbVie Deutschland GmbH & Co. KG, University of Tampere, European Commission, Massachassuetts Medical Society and American Academy of Allergy, Asthma and Immunology. SW reports grants and personal fees from AstraZeneca, GSK, Boehringer-Ingelheim , Genentech, Sanofi-Regneron, and Novartis and personal fees from Knopp. HJZ has nothing to disclose. AB has nothing to disclose.

ACKNOWLEDGMENTS

No sponsorship was sort or received. We thank the Lancet for making their offices available for a Commissioners meeting in May 2016. Commissioners covered their own travel and accommodation expenses to attend this meeting.

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Legends to Figures

Figure 1: ~~Asthma~~ Crude asthma ~~death~~ mortality rates 1960-~~2013~~2012 for the 5-34 age range in 46 countries and the two main eras of asthma management. The locally weighted scatter plot smoother rates with 90% confidence intervals, weighted by country population, are shown in red. The association of the inflammation based era with improved outcomes can readily be observed, as can the flat-line with regard to further improvements since ~~the millenium~~2005.

Figure 2: ~~Asthma prevalence (%) in 13-14 year olds~~Prevalence of symptoms of asthma in the last 12 months among people aged 18-40 around the globe (World Health Survey 2002-3)[84].

Figure 3: Comparative effect sizes expressed as odds ratio for asthma exacerbation rates for the use of mepolizumab 250mg IV for asthma, when applied using control-based paradigm (Unselected), and when used in a targeted therapy paradigm in patients with severe eosinophilic asthma (Targeted)[109]. Significant benefit in an important subgroup is missed if all comers are treated

Figure 4: Different pathways leading to eosinophilic airway inflammation.

Figure 5: GINA 2014 asthma management guidelines

Figure 6: Ongoing monitoring of the two dominant components of airways disease and precision management. *Rapid onset beta-agonist/ICS combination is the default rescue medication

Figure 7: Patterns of airway disease through the ages with main ~~components~~traits. Gaps indicate no data

Figure 8: Hypothesis 1. The relative risk contribution to later asthma is composed of a multitude of small effects. The small effects originate from various subsystems or compartments (e.g. immune system, airway growth, epithelial function, etc.). Each compartment or subsystem has its own timing and phase of development. Their relative importance for asthma (arrows) may be age- dependent. Vulnerability (window of opportunity) to environmental stimuli will likely vary at different age periods in each compartment. The overall temporal evolution of health and disease will be affected by the complex temporal interplay of all these compartmental subsystems.

Figure 9: Hypothesis 2. Since not all compartments of the respiratory system mature at the same age, the relative contribution (expressed in circle diameter) of each compartment (C1 to C5) to the overall behaviour of the normal, but also abnormal, function of the respiratory system may change during development. E.g. the relative importance of small airway size will (exemplified by compartment C2) diminish with age for wheezing disorders, whereas other key compartments, e.g. the immune system in the sensitized child, will become dominant or even critical with increasing age (exemplified by compartment C5).

Figure 10: Hypothesis 3. Depending on how environmental stimuli affect or even alter the development of the various compartments, the phenotypical expression of the disease may be different as well as age-dependent. E.g. Savinjie et al[46] demonstrated that risk factors for transient or intermediate onset asthma are qualitatively similar, but quantitatively different than for

persistent asthma. Illustrated in this model, the relative contribution to the overall disease risk of small airway size (C2) and sensitization to any allergen (C5), respectively is quantitatively different in transient wheeze (phenotype 1) than for persistent wheeze (phenotype 3). Very likely, in a large population of asthmatics, there will be overlaps between distinct asthma phenotypes.

Biomarker	Association with treatment response	Invasiveness	Comments
FeNO	Corticosteroids, anti-IL-13, anti-IL-4&13, anti-IgE	Non-invasive	Easy, quick, not specific, cheap, generally available. Loses specificity in smokers[332]
Serum IgE	Not associated	minimal	Although recommended to measure, there is no clear association between IgE or allergy as a biomarker of treatment responses or clinical outcome[289]
Serum Periostin	Anti-IL-13, anti-IgE	minimal	Effect shown with Anti-IL-13, limited availability currently. Confounded by growth in childhood, pregnancy and dental disease[333]
Blood eosinophil count	Anti-IL-5, anti-IL4/13 (?)	minimal	Generally available, high clinical impact, predicts anti-IL-5 response and ICS response in COPD[101]. Associated with increased risk of lung attacks[100,101]
Sputum eosinophil count	Corticosteroids, Anti-Il-5, anti-IL4/13 (?)	moderate	Specialist centres, tissue specific, time-consuming. Good therapeutic marker for ICS, OCS, biologics. Established evidence of value as a monitoring tool

Table 1. Potential biomarkers of eosinophilic airway inflammation. FeNo= fraction of exhaled nitric oxide; IgE = immunologulin E

Area	Drugs (number)	Market entry profitability			Cumulative
		PHASE II	PHASE III	Approved	
HIV/AIDS	108	75	50	39	14
Dermatology	122	8	44	29	11
Haematology	163	60	4	22	9
Neurology	192	73	47	22	8
Cancer	68	78	46	20	7
Cardiovascular	280	69	4	22	6
Respiratory	165	68	31	16	3

Table 2. New drug discovery in different fields of medicine[19]. Figures represent percentage unless otherwise indicated.

Monoclonal antibody	Biomarker used for patient selection	FEV[1]	AHR	ACQ	Exacer-bations	OCS - sparing effect	QLQ	Blood eos.	Sputum eos.	FeNO	Serum IgE	Comments
		Effect on clinical endpoints						Effect on biomarkers				
Anti-IL-5	PB and sputum eos. count, exacerbation rate.~~,~~	+	0	+	++	++	++	↓↓	↓	0	0	Clinical effects in specific subgroup of severe asthma
Anti-IgE	Blood IgE*, spec. IgE level and positive SPT*, FeNO*, ~~periostin~~blood eosinophils*	+	0	+	++	unclear	+	↓	↓	↓↓	0	Most RCT's focused on moderate to severe asthma, ~~sparse~~ less evidence in very severe asthma
Anti-IL-13	Periostin level, FeNO	+	unclear	+	+	N/A	0	↑	unclear	↓↓	↓	Partially based on subgroup analysis
Anti-IL-4/IL-13	Periostin, FeNO and blood eos., ,	+	unclear	unclear	++	unclear	N/A	↑	unclear	↓↓	↓↓	Promising agent potentially offering more efficacy than achieved with single cytokine blockade[334]

Table 3. Effect of Type 2 associated monoclonal antibodies on clinical markers and biomarkers in severe eosinophilic asthma. *Not yet used for patient selection but shown to be highly predictive of a response.

+ = clinically improved; 0 = measured and no effect observed; N/A = not attributable/not measured; unclear = measured, not enough data points for conclusion. Exp, expected; FEV1, Forced Expiratory Volume in 1sec.; AHR, airway hyperresponsiveness; ACQ, asthma control questionnaire; OCS, oral corticosteroid; ICS, Inhaled corticosteroid; QLQ, quality of life questionnaire; eos., eosinophils; FeNO, fraction of exhaled nitric oxide; IgE, Immunoglobulin E; RCT, randomised controlled trial; IL, Interleukin.

		Recognition	Treatments	Likely impact of treatment	Factors associated with better treatment response	Comments
Variable	ASM contraction	$FEV_1/FVC < LLN$ Bronchodilator reversibility and short-term PEF variability consistent with variable airflow obstruction and large component of ASM contraction ICS/OCS response consistent with inflammation related airflow limitation (i.e. mucosal oedema, mucuse plugging) Loss of airway support probable if imaging or physiological evidence of emphysema	$Beta_2$-agonists (SABA and LABA) Antimuscarinic agents (i.e. LAMA) Theophylline Bronchial thermoplasty? Loss of airway support may respond to lung volume reduction strategies	**Patient related:** Symptom scores QOL Small reduction in attacks (particularly less severe) Exercise capacity **Surrogate:** FEV_1 PEF Airway responsiveness	Acute bronchodilator response Airway hyperresponsiveness Eosinophilic airway inflammation	Different classes of bronchodilators have additive effects Bronchodilator therapy increases probability of patients discontinuing ICS. Do not use in separate inhalers in patients with eosinophilic airway inflammation ~~and/~~or those who might have variable symptoms and inflammation Underlying causes of airflow limitation will not be definable in many. 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.
	Mucosal oedema					
Airflow limitation	Mucus plugging					
	Loss of airway support					
Fixed	Small airway fibrosis					

Eosinophilic airway inflammation	See table 1	ICS and OCS See table 3	**Patient related:** See table 3 **Surrogate:** See table 3	See table 1&3	Different biomarkers provide complimentary information[100] Suspect episodic inflammation in patients with episodic symptoms Some 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 (i.e. long-term low dose macrolides) Inhaled interferon-β (viral infection) Influenza vaccination Antifungal drugs (?only effective in those sensitised ~~and~~ to aspergillus and colonised)	**Patient related:** Reduced attacks Symptom scores QOL **Surrogate:** Small improvement in FEV_1 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/OCS Stop ACE inhibititor	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Cough senstivity	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 middle aged females Sometimes due to factors in table 5

Table 4. Treatable traits of airway diseases

Component	Recognition	Treatments	Likely impact of intervention	Factors associated with better treatment response	Comments
Rhinitis/gastrooesophageal reflux/	Suggestive symptoms Imaging Oesophageal manometry	Nasal steroids PPI	**Patient related:** Symptom scores QOL **Surrogate:** Improved imaging appearances Nasal inspiratory flow Oesophageal manometry	Chronic rhinitosinusitis with polyps can be difficult to control with nasal steroids	Causes of asthma-like symptoms but direct link with lower airway disease unlikely
Obesity/deconditionoing	BMI Cardiorespiratory exercise test	Weight loss Bariatric surgery Rehabilitation/exercise training	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Reduced BMI Improved 6 minute walk test	Absence of co-morbidity Good social support Group participation	Bariatric sugery most effective intervention for obesity Link with lower airway disease poorly understood
Anxiety/dysfunctional breathing/vocal cord dysfunction	Disproportionate breathlessness, air hunger Frequent sighs Dizziness, light headed, tingling hands and face Chest tightness Inreased Nijmegen questionnaire score Noisy inspiration	Physiotherapy Rebreathing Anxiolytics Counselling Speech therapy	**Patient related:** Symptom scores QOL	Early recognition	Important but poorly understood causes of morbidity

Depression	Hospital anxiety and depression scale	Antidepressants	**Patient related** Symptom scores	May be associated with increased risk of death	Particularly important in severe disease
Treatment associated morbidity	ACE-inhibitor associated cough Breathlessness/tiredness secondary to β-blocker	Withdraw or replace treatment	**Patient related:** Symptom scores QOL Cough frequency **Surrogate:** Reduced cough sensitivity Improved 6 minute walk test	ACE-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 and/or risk factors Restrictive spirometry Abnormal CXR and/or CT	Of the underlying condition	Specific to underlying condition	Treatable condition	Cardiac disease commonly coexists and can be difficult to tease apart relative contributions

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

Component	Recognition	Treatments	Likely impact of intervention	Factors associated with better treatment response	Comments
Smoking and other environmental exposures	History Urinary cotinine Exhaled CO	Cessation Treatment for nicotine addiction (NRT, Varenicline)	**Patient related:** Symptom scores QOL Reduction in attacks Exercise capacity Increased survival **Surrogate:** FEV_1 PEF Neutrophilic airway inflammation Reduced decline in lung function	Smoking history Addiction potential (?genetic) Presence of pre-existing lung disease	Difficult to modify Treatments for nicotine addiction doubles chances of sustained quitting Impact 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 (i.e. latency) Relevant exposures Skin prick tests/RAST tests	Avoidance Desensitisation ICS and OCS Omalizumab ? Air filtration systems	**Patient related:** Symptom scores QOL Reduction in attacks Remission **Surrogate:** FEV_1 PEF Airway responsiveness Eosinophilic airway inflammation	Good evidence of sensitisation Monosensitisation Early recognition	Limited evidence base Timing of intervention may be critical May be epiphenomenon
Treatment adherence and device related factors	Prescription refill rates Drug levels FeNO supression test Chipped inhalers	Counselling and education Better inhalers Maintenance and reliever therapy with ICS/SABA or ICS/LABA (MART) Mobile/IT reminder technology	**Patient related:** Reduced attacks Symptom scores QOL Reduction in attacks **Surrogate:** Improvement in FEV_1 Reduced sputum eosinophils and FeNO	Poor inhaler technique more tractable than adherence issues	Common but difficult to detect and modify

Social and behavioural issues	Social history Home visit School/workplace information	Support	**Patient related:** Symptom scores QOL		Difficult to modify, particularly in adults

Table 6. Important environmental and behavioural factors potential associated with asthma-like symptoms

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Figure

Figure 1

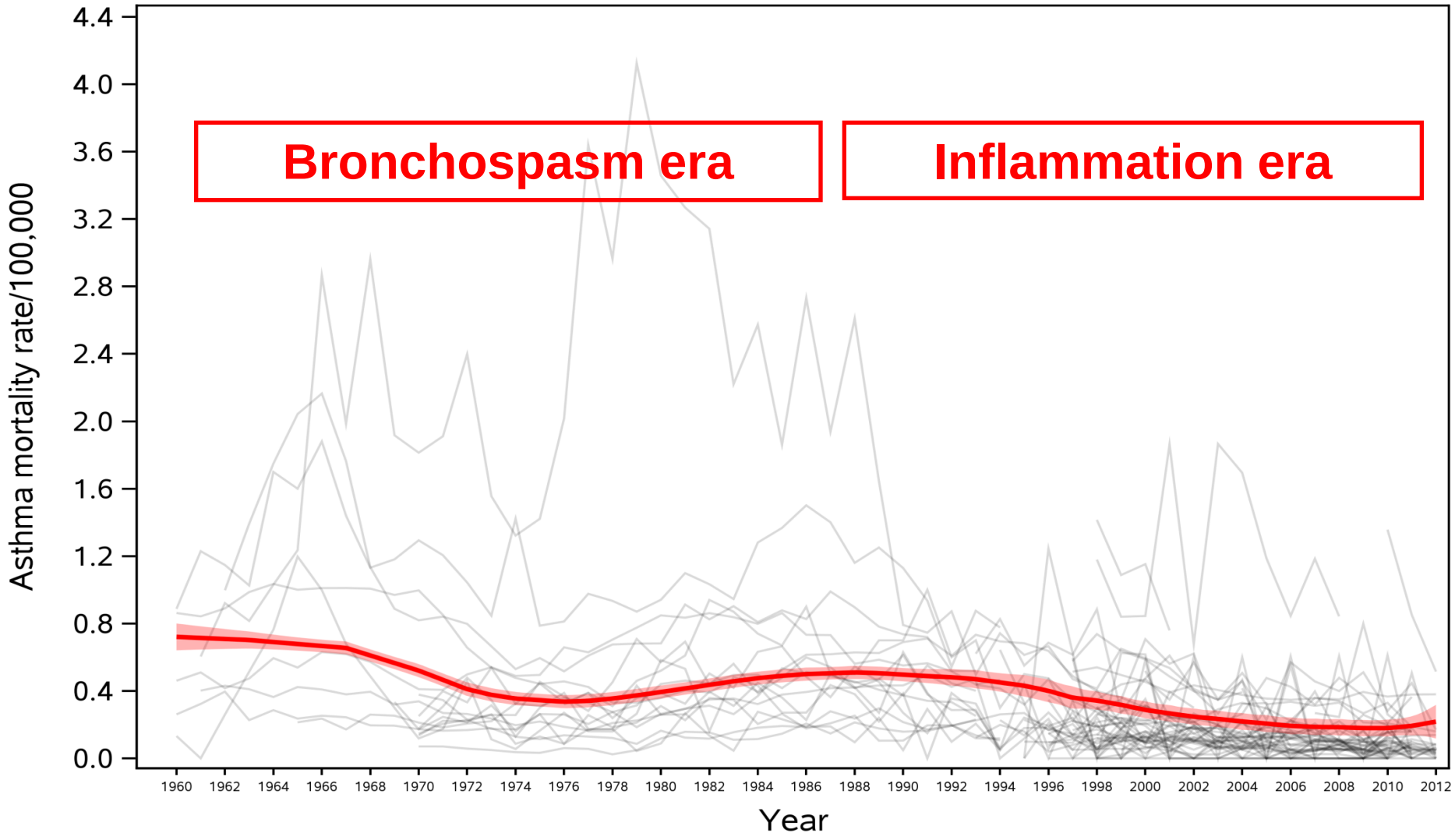
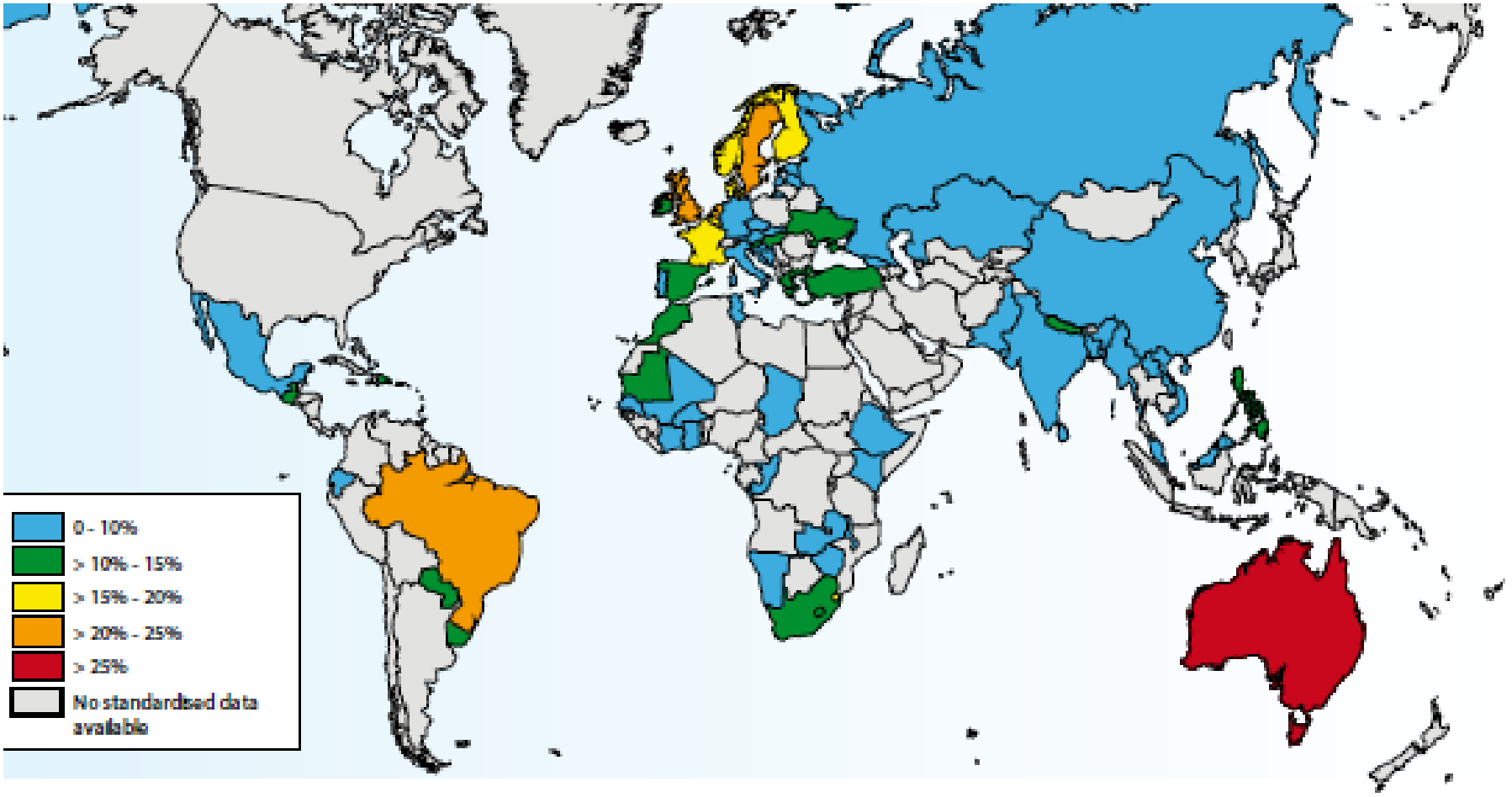


Figure 2



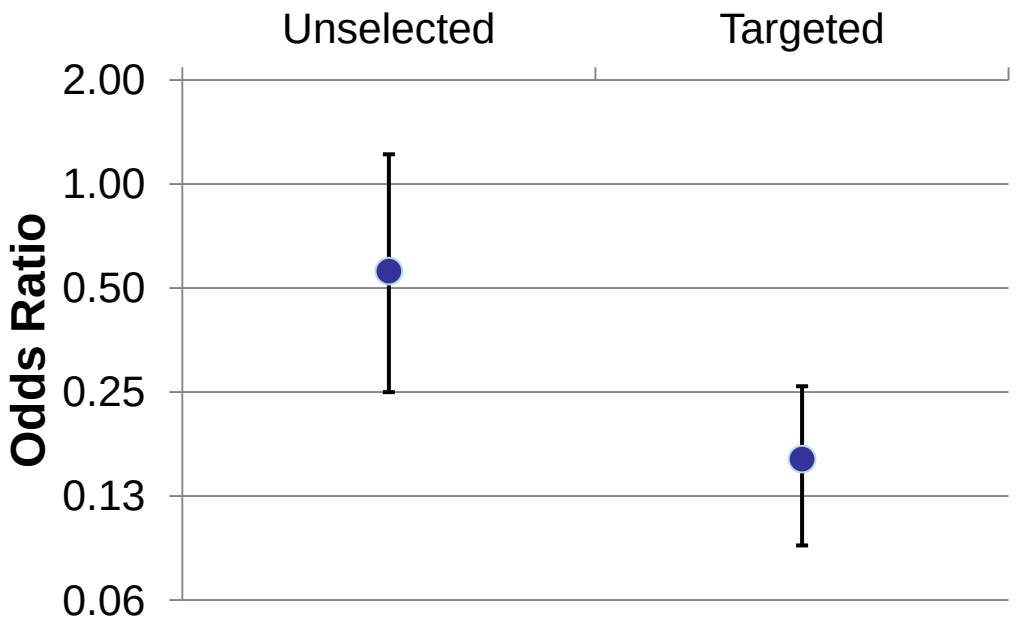


Figure 3

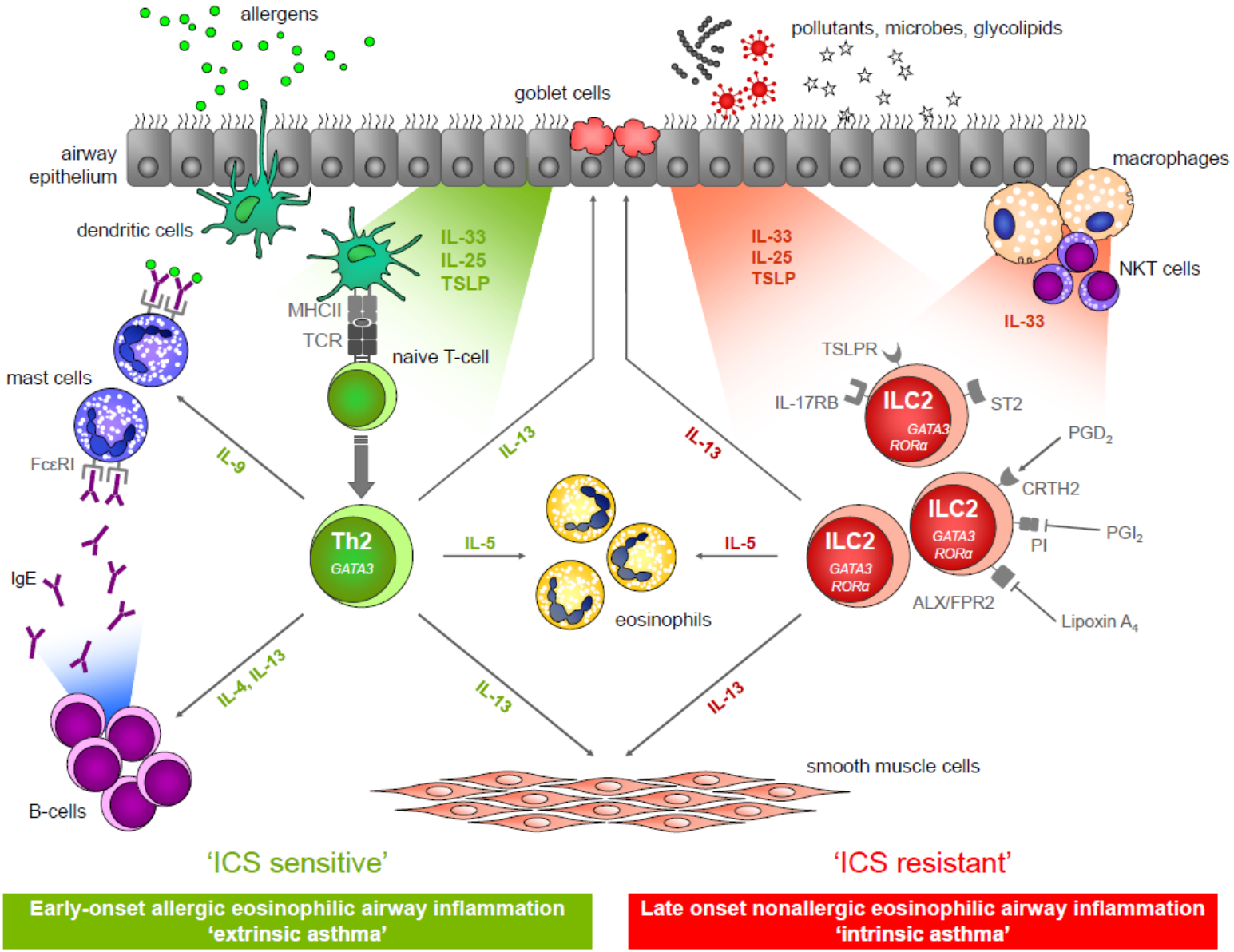
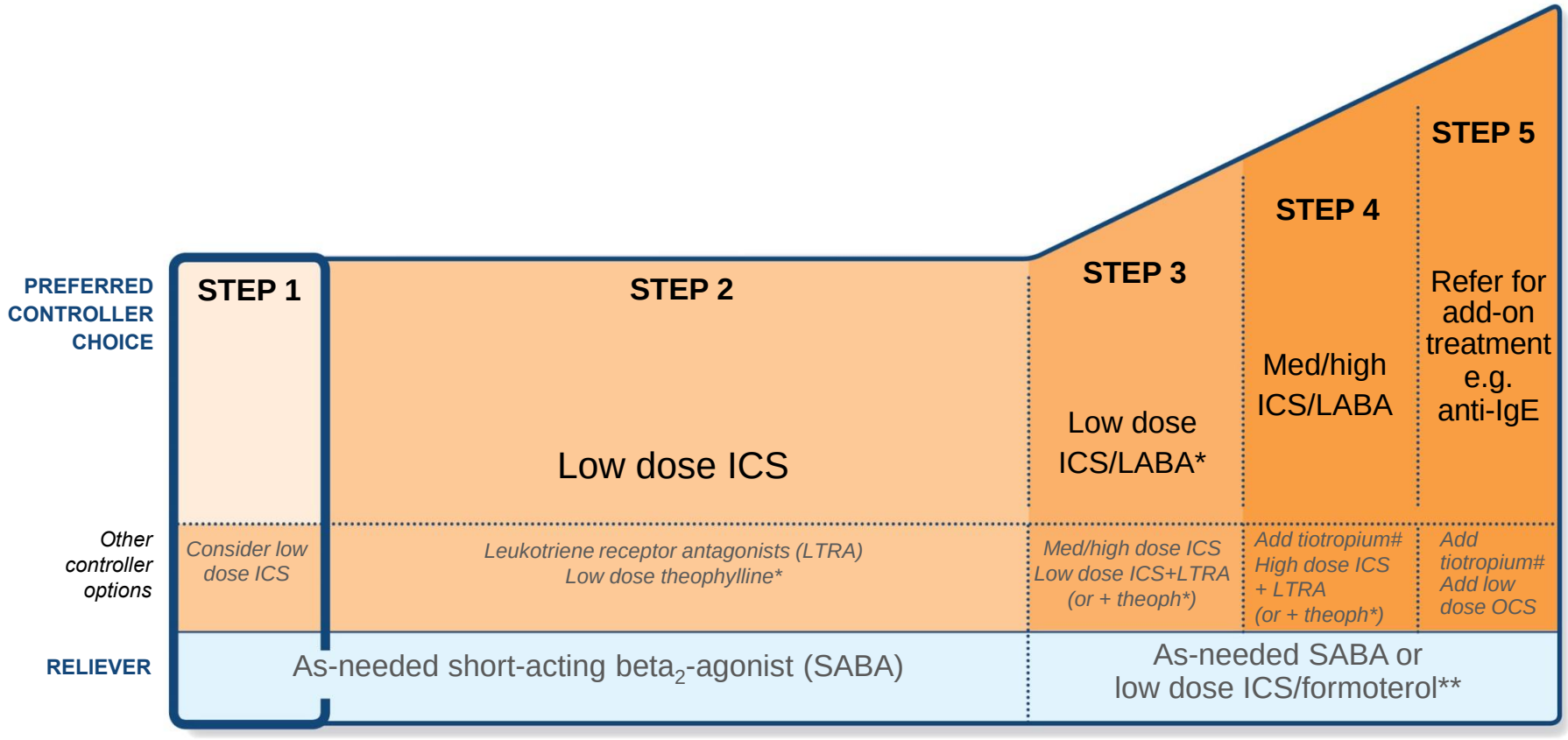


Figure 4
Two pathways leading to eosinophilic airway inflammation

GINA guidelines 2014



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

Figure 5

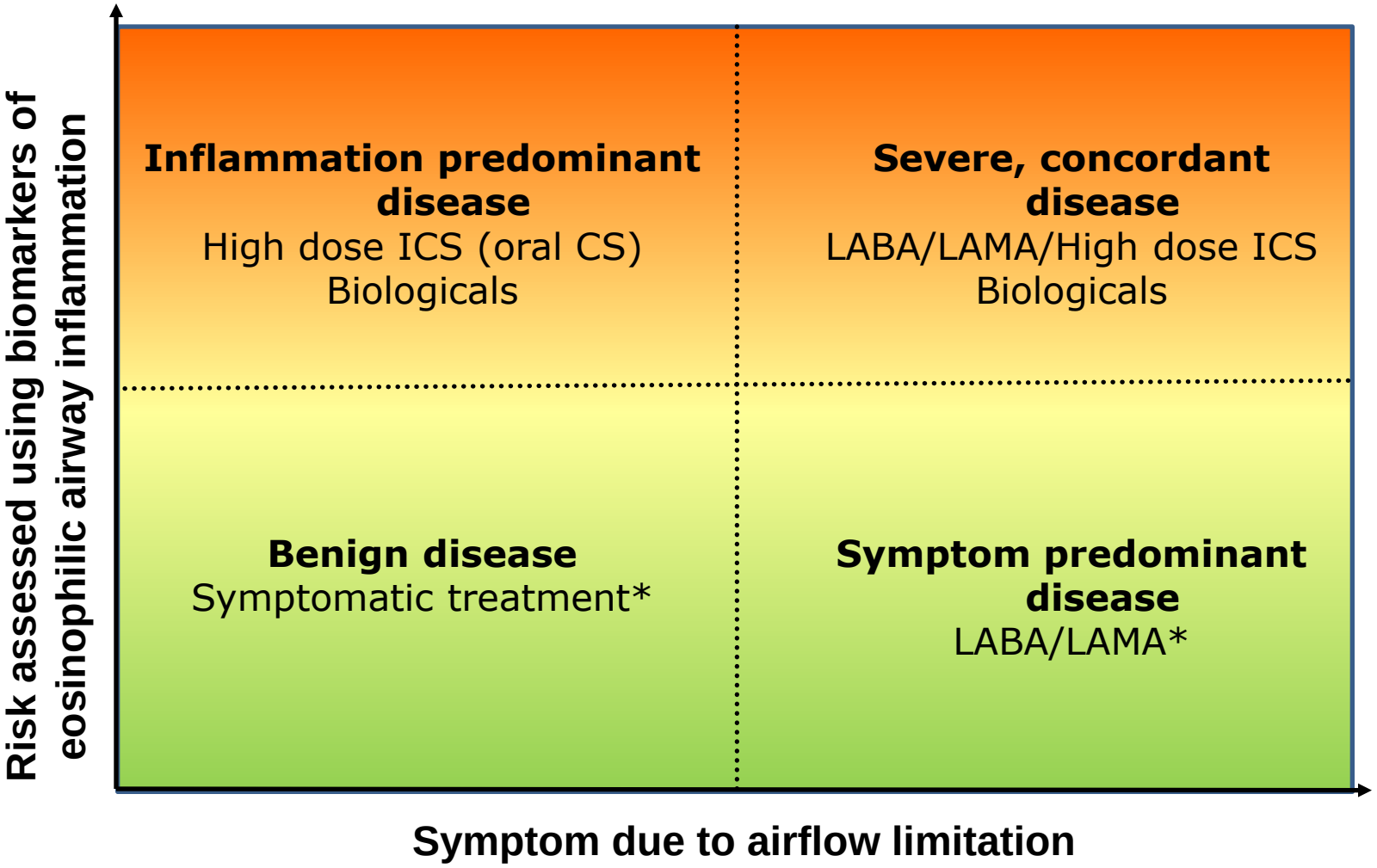
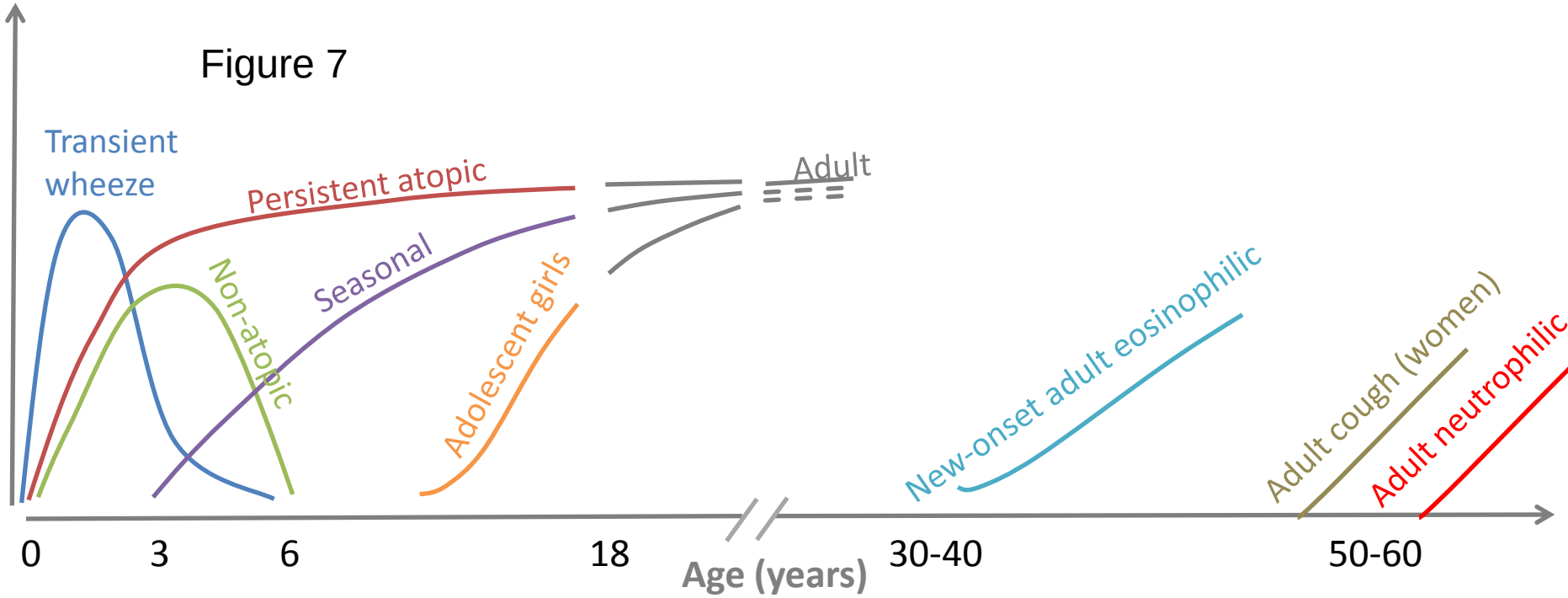

Risk assessed using biomarkers of eosinophilic airway inflammation
Inflammation predominant disease
High dose ICS (oral CS)
Biologicals
Severe, concordant disease
LABA/LAMA/High dose ICS
Biologicals
Benign disease
Symptomatic treatment*
Symptom predominant disease
LABA/LAMA*
Symptom due to airflow limitation

Figure 6

Figure 7



Trait		Transient wheeze	Persistent atopic	Non-atopic	Seasonal	Adolescent girls	New onset adult eosinophilic	Adult neutrophilic	Adult cough (women)
Variable	ASM contraction	+	++		++		+	+	0
	Mucosal oedema	++	+		+		++	+	0
Airflow limitation	Mucus plugging	++	+		+		++	++	0
	Small airway fibrosis	0	0				+	++	0
Fixed	Loss of airway support	+	0				0	++	0
Eosinophilic airway inflammation		0	++		+		+++	+	+*
Cough reflex hypersensitivity		++	+		+		++	+	+++

Figure 8

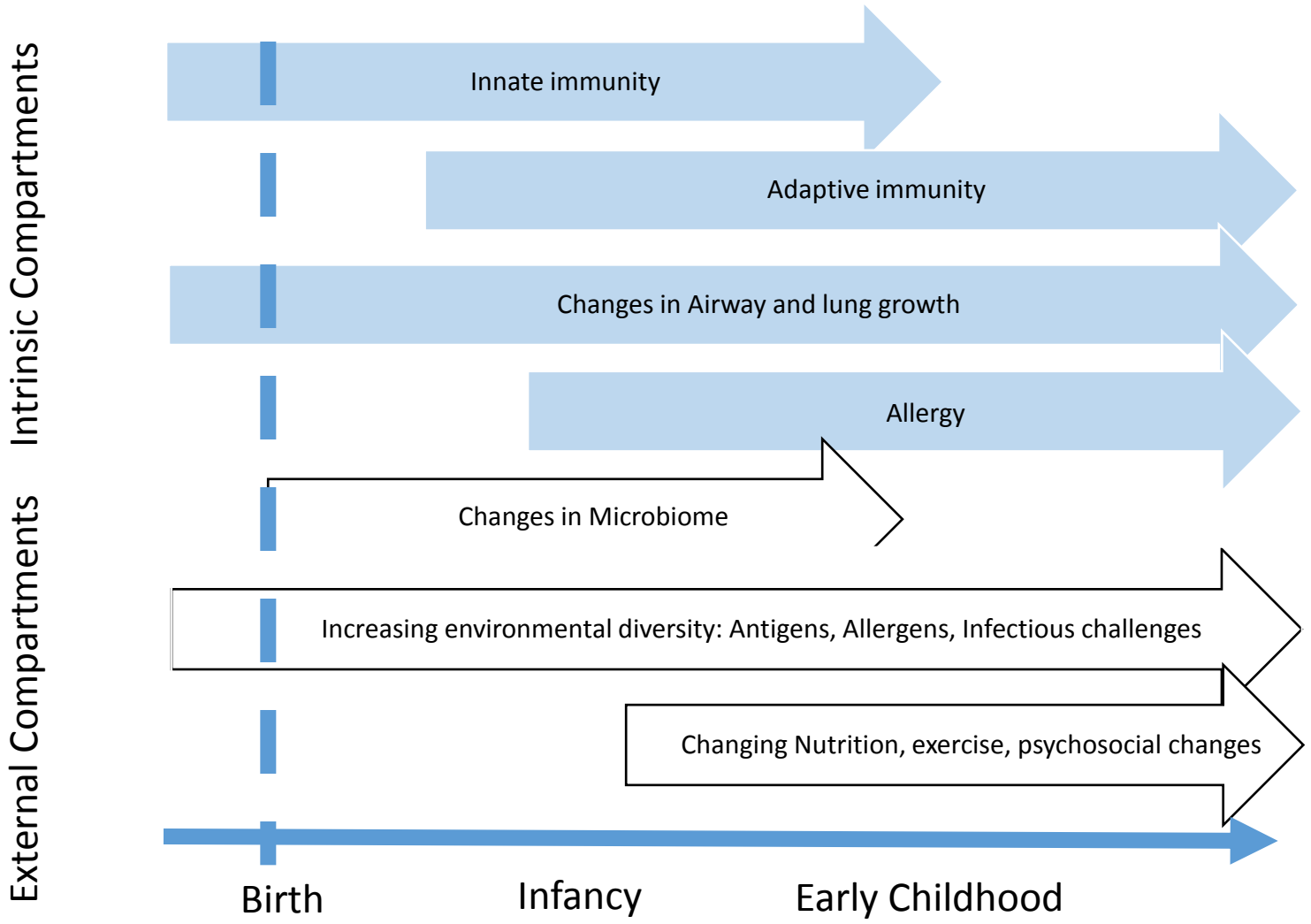

Intrinsic Compartments
External Compartments
Innate immunity
Adaptive immunity
Changes in Airway and lung growth
Allergy
Changes in Microbiome
Increasing environmental diversity: Antigens, Allergens, Infectious challenges
Changing Nutrition, exercise, psychosocial changes
Birth
Infancy
Early Childhood

Figure 9

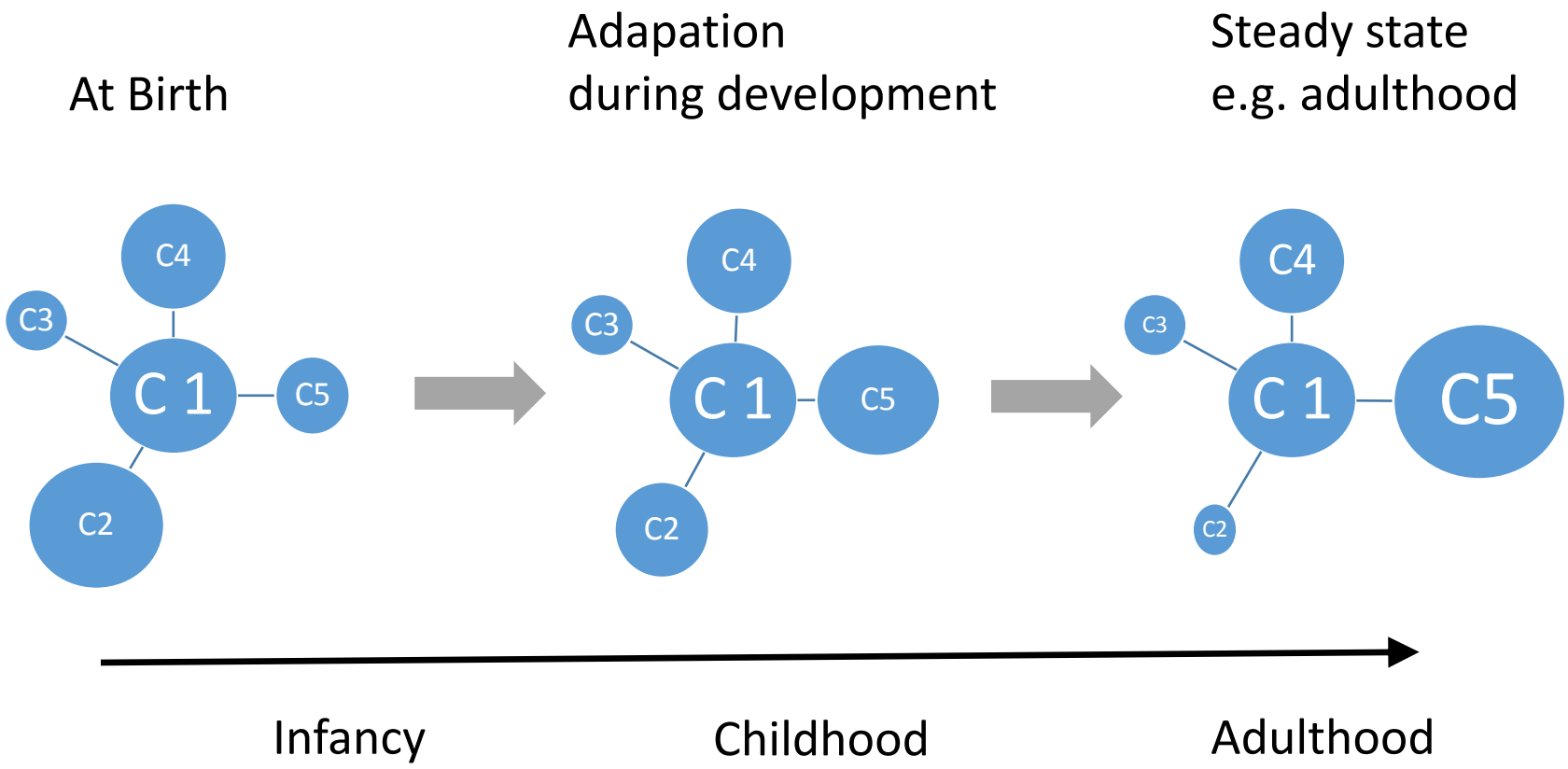
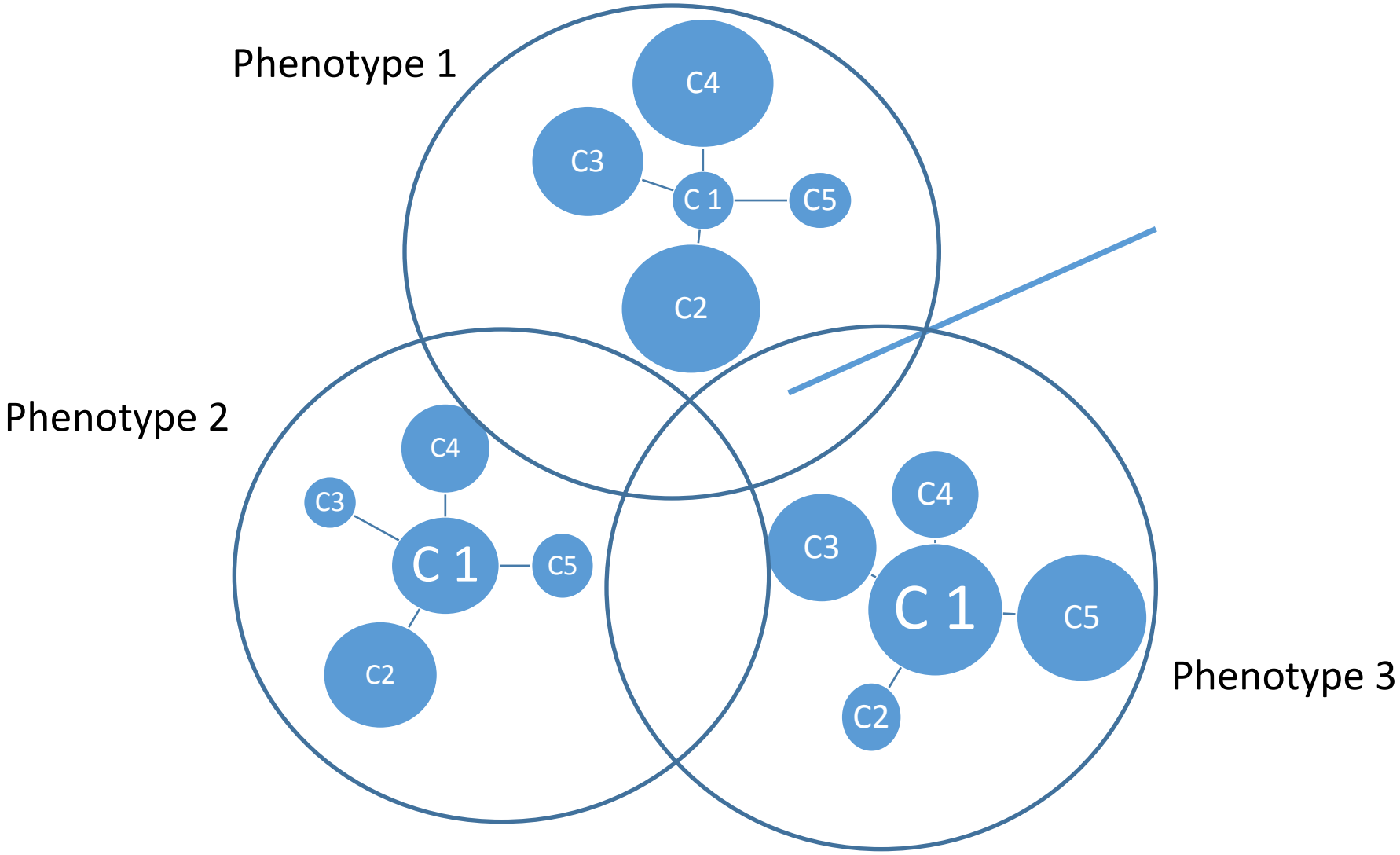

At Birth
Adapation
during development
Steady state
e.g. adulthood
C4
C3
C 1
C5
C2
C4
C3
C 1
C5
C2
C4
C3
C 1
C5
C2
Infancy
Childhood
Adulthood

Figure 10


Phenotype 1
C4
C3
C 1
C5
C2
Phenotype 2
C4
C3
C 1
C5
C2
C4
C3
C 1
C5
C2
Phenotype 3

Table

Box 1. Summary of recommendations

1. A revolution in thinking about asthma, generalizable to all airway diseases and delivering precision medicine.

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

2. Move beyond a disease control-based ambition for asthma treatment.

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

3. Break out of our age- and discipline-related silos.

- See airway disease in the context of the developmental track 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 aging.
- Regulators should enforce existing guidelines for mandatory testing plans for children as part of licensure process for new asthma drugs.

4. Test before treat:

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

5. Zero tolerance for attacks.

- Replace the inadequate terms 'exacerbation' or 'flare-up' with 'attack'
- Precision medicine rather than 'one size fits all' approach to treatment and secondary prevention of attacks.
- Development of a risk score and incorporation into everyday 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 SABA with inhaled corticosteroid (ICS)/fast-acting β_2-agonists as reliever therapy in patients with episodic symptoms, with no escalation of ICS dose unless biomarkers of eosinophilic disease/ICS responsiveness are present

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

- Move from a traditional disease category/symptom/lung function based assessment of treatment need and response to one where 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 it.
- Ensure biological agents agents are used effectively in individual carefully characterised patients.
- Tackle the 'which biological for which patient' question by collating phase 2 and 3 clinical trial data and carefully collected post-registration patient data with the goal of identifying responsive sub-groups, with prospective validation of the findings.

7. Better research.

- Deliver more treatment to the right lungs rather than more treatments to more lungs by working in collaboration with pharma to ensure that future clinical trials establish not only treatment efficacy and safety but identify definable sub-groups 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.
- Test before you research. 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 unpicking the complex interplay between different inflammatory pathways, defining why aberrant inflammatory pathways perpetuate and identifying preventive strategies.

Box 2. The Commissioners

CHANGING THE WAY WE THINK ABOUT AIRWAYS DISEASE: Ian Pavord, Richard Beasley, Alvar Agusti, Peter Gibson, Francine Ducharme, Guy Marks, Guy Brusselle, Andy Bush

BEYOND GUIDELINES. OPERATIONALISING INDIVIDUALISED TREATMENT IN DIFFERENT HEALTH CARE SETTINGS: Richard Beasley, Ian Pavord, John Fahy, Sally Wenzel, Liam Heaney, Elisabeth Bel, Heather Zar, Marc Humbert, Andy Bush

WHEEZING ILLNESSES ACROSS THE AGES: Urs Frey, Andy Bush, Alvar Agusti, Paul Cullinan, Francine Ducharme, Peter Sly, Fernando Martinez, Erika von Mutius

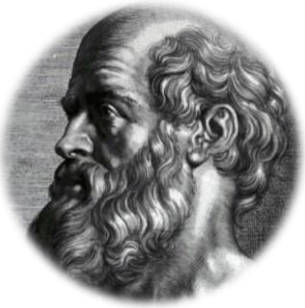
TREATMENT OF THE ASTHMAS – BEYOND PALLIATIVE CARE: Pat Holt, Andy Bush, Peter Sly, Erika von Mutius, Gary Anderson, Clare Lloyd, Paul Cullinan, Fernando Martinez, Adnan Custovic

TARGETING ASTHMA ATTACKS: Ian Pavord, Andy Bush, Richard Beasley, Peter Gibson

GETTING SERIOUS ABOUT SEVERE DISEASE: Liam Heaney, Sally Wenzel, Elisabeth Bel, Marc Humbert, Guy Brusselle, Ian Pavord, Andy Bush

IMPROVING RESEARCH: ***Clinical Trials:*** Richard Beasley, Ian Pavord, Andy Bush. ***Epidemiology*** Richard Beasley, Erika von Mutius, Paul Cullinan, Fernando Martinez, Guy Marks, Urs Frey, Heather Zar, Adnan Custovic , Paul Cullinan, Peter Sly. ***Animal models***: Clare Lloyd, Guy Brusselle, Pat Holt, John Fahy, Gary Anderson

Box 3. Asthma definitions throughout history

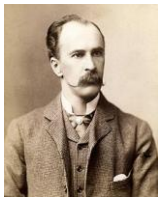


4th century BC: The Corpus Hippocraticum. ‘Aazein’ = to pant. Ailments characterised by spasms of breathlessness occurring more frequently in anglers, tailors and metal workers

Maimonides 12th century AD: Patient's symptoms often started as a common cold during the wet months. Eventually the patient gasped for air and coughed until phlegm was expelled. He noted that the dry months of Egypt helped asthma sufferers.

Sir John Floyer 1698: When the Muscles labour much for Inspiration and Expiration thro' some Obstruction, or Compression of the Bronchia, etc. we properly call this a Difficulty of Breath: but if this Difficulty be by the Constriction of the Bronchia, 'tis properly the Periodic Asthma: And if the Constriction be great, it is with Wheezing; but if less, the Wheezing is not so evident.

Henry Hyde Salter (1882): Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks



Sir William Osler (1892): highlighted the following features: spasm of the bronchial muscles; swelling of the bronchial mucous membrane; a special form of inflammation of the smaller bronchioles; similarities with hay fever; running in families; often beginning in childhood and sometimes lasting into old ages; symptoms occurring in a variety of circumstances which at times induce a paroxysm; a relationship with climate, atmosphere (i.e. hay, dust, cat), violent emotion, diet and colds; and distinctive sputum containing rounded gelatinous masses ("perles") and Curschmann spirals & octahedral crystals of Leyden.

Ciba symposium 1959: Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease.

GINA 2002: Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread airflow obstruction that is typically reversible either spontaneously or with treatment.

GINA 2014: Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Box 4. Salter's description of asthma and its impact on the individual

'…. 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.'

Box 5. Conflicting recommendations from guideline groups of use of exhaled nitric oxide (FeNO) to diagnose and manage asthma

GINA 2014

FeNO is increased in eosinophilic asthma but also in non-asthma conditions (eg. eosinophilic bronchitis, atopy, atopic rhinitis) and has not been established as being useful for making a diagnosis of asthma. …. There are no long-term studies examining the safety of withholding ICS in patients with asthma and low FeNO. Consequently it cannot be recommended at present for deciding whether to treat patients with possible asthma with ICS.

ATS clinical practice guideline 2011

We recommend the use of FeNO in the diagnosis of eosinophilic airway inflammation….. We recommend the use of FeNO in determining the likelihood of steroid responsiveness in patients with chronic respiratory symptoms possibly due to airway inflammation.

BTS/SIGN guidelines 2014

Paediatrics: It is feasible to measure FENO in unsedated children from the age of 3–4 years. A raised FENO is neither a sensitive nor a specific marker of asthma with overlap with children who do not have asthma……. At present, there is insufficient evidence to support a role for markers of eosinophilic inflammation in the diagnosis of asthma in children. They may have a role in assessing severity of disease or response to treatment.

Adult: An alternative and promising approach to the classification of airways disease is to use tests which best identify patients who are going to respond to corticosteroid therapy. A raised sputum eosinophil count and an increased FENO are more closely related to corticosteroid response than other tests in a variety of clinical settings. There is also evidence that markers of eosinophilic airway inflammation are of value in monitoring the response to corticosteroid treatment.

Box 6. ERS/ATS 2014 definition of severe asthma

Definition of severe asthma for patients 6 years old and above

Asthma which requires treatment with guidelines suggested medications for GINA Stages 4-6 asthma (high dose inhaled CS* and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.

I. Uncontrolled asthma defined as at least one of the following:

- Poor symptom control: ACQ consistently >1.5, ACT ≤19 (or "not well controlled" by NAEPP/GINA guidelines)
- Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year
- Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year
- Airflow limitation: after appropriate bronchodilator withhold FEV1< 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)

II. Controlled asthma that worsens on tapering of these high doses of inhaled CS or systemic CS (or additional biologics)

* The definition of High dose ICS is age-specific

Abbreviations: ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; CS: Corticosteroids; GINA: Global Initiative for Asthma; LABA: long-acting 2-agonists; NAEPP National Asthma Education and Prevention Program.

***Reply to Reviewers Comments**

Thank you for your revised version of the Commission. I have sent it again to one of the previous reviewers and two new ones. See their comments below. We have also discussed it again in our editorial meeting and Richard Horton has looked at it separately as well. We think we are now nearly there with this Commission and would like you to revise once more taking the following points into account (I will discuss with you in person as well for further clarification if needed):

1) The Executive summary needs to change. There is no need to describe the process of the Commission. We need, however, a true summary and also the recommendations upfront. There could be, for example, a key messages panel summarizing the one or two important messages from each of the seven chapters, and the recommendations in the same panel. Remember that some people will only read the executive summary.
We have revised the executive summary extensively, removing test related to the process and focusing much more on the opinions and recommendations. We have added a new box (box 1) summarising the key recommendations.

2) The unevenness of the report that some reviewers pointed out could be remedied by having more subheadings in some of the chapters and carefully look at redundant language and perhaps also try to minimize the unnecessarily confrontational style further. For example, we would like you to change your headings to 'Where are we now?@ and 'Where do we need (or want but consistently) to go'.
We have made greater use of subheadings, addressed the confrontational style and reduced redundant language. Many of these changes are in the first two sections, where we believe these issues most apply. We have also adopted the two main subheadings you have suggested (i.e. 'Where are we now?' and 'Where do we want to go?'). We feel that these changes have improved the flow of the manuscript.

3) I was wondering if the guideline section needs a bit more on how the current guidelines are developed and applied in the 'where are we now' section, but leave that up to you to decide.
We think this is an excellent suggestion and have added a short section and a new box dealing with the providence, scope and development of the guidelines and how this might have become a problem (see page 25).

4) Some of the reviewers' points still merit a response and some minor revision, perhaps, but again up to you to decide. We don't need to be too careful or timid.
We found this round of reviewers' comments very helpful and we have done our best to respond to all of their points (see below), without being too timid (!).

5) I need a contributor statement and a summarized conflict of interest statement at the end of the text.
Provided.

6) We need authorship and ICJME CoI forms for all authors
These are now provided

7) All figures should be in editable format
Done

We think that the next version will likely be ready to accept and I am very keen that we aim for launch/publication for ERS in Milan. For this I would need a revised version with all these points addressed by end of February.

I look forward to speaking with you

Best wishes,
Sabine

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UK
Tel: +44 207 424 4933

COMMENTS TO THE AUTHOR:

Reviewer #3: General Comments:

There is still a confrontational use of language that may detract from the acceptance and the serious sense of purpose.
We have moderated this as best we can (see above). However, we would respectfully point out that our remit was to be challenging of current dogms

Specific Questions in Response are Underlined:

The statement about reducing corticosteroid exposure refers specifically to oral corticosteroid use. Has this been made clear?
We think this refers to the sentence at the end of the 'Make the most of new treatment opportunities in severe disease' section on page 70-71 of the marked copy. We have been very careful to emphasise that this refers to oral corticosteroids only.

P31 - Will patients comply with these recommendations?? Daily use of ICS for those only having symptoms twice a month? Building all inhalers with bulky spacers?
This important issue is dealt with in the severe asthma section.
Where and how?
We can see that we had not addressed this issue adequately. We have added the following sentence to the 'Better monitoring' section on page 33: 'We need research to better understand patients' attitudes and response to these devices and this type of monitoring'.

Have the cross section data regarding differences between home vs hospital and vaginal vs. C section been reproduced?
This is not a systematic review. See response to reviewer 2's point e.
The statement is made as if it is a corroborated fact.
We have modified this statement to: **'**Place (home vs. hospital[183]) and mode (vaginal vs. Caesarian section[56]) of delivery **may** impact the risk of future airway disease' (top page 37 of marked version).

Reviewer #4: I was invited to serve as an additional reviewer to this commissioned report on asthma. I had the benefit of reviewing the comments made by several prior reviewers and the response. In essence the commissioned report is designed to prompt a change in thinking by providing a new overriding message, forward vision, actions/recommendations, and its afterlife.

The authors are to be congratulated for assembling a knowledgeable panel of experts and organizing a sizeable document to summarize those thoughts. The document is informative and summarizes some key messages that are making their way through the literature. Those new findings are already prompting a change in management. I suspect that a core group led this effort and took responsibility for assembling the document while others provided input. Nevertheless, there is an apparent difference in style throughout the document that leads to some inconsistency in the presentation. Some have nice breaks in the text with bullet points and others are all text and somewhat of a stream of consciousness covering various topics. I also thought the prior reviewers made some excellent points but some of those points do not appear to be addressed in this current revision, one of them being the inconsistency in format.
We have done our best to address this valid concern (see response to editor's second point).

A few general comments:
1. **Much of the change proposed centers around new information obtained around the recent information and discussion generated around anti-IL5 and eosinophils as a biomarker to predict response.**
2. **There is considerable information available about anti-IgE and new insights into mechanisms of effect, advantages in preventing exacerbations, and approval down to 6 years of age.**

We agree but feel that the story of the clinical development of Mepolizumab best demonstrates the problems imposed by current airway disease taxonomy. It remains the case that Omalizumab is a treatment targeted at a population identified by measures not linked to treatment efficacy (i.e. serum IgE, weight, atopy), a point we make in the severe asthma section. We feel that this would be a poor example of the sort of precision, targeted treatment we call for.

3. **There is a fair amount of finger-pointing in the review as reasons for some lack of change in asthma management. However, the authors provide an excellent figure (figure 1) showing the reduction in asthma deaths. We have also seen a remarkable reduction in oral steroid therapy as maintenance therapy over the past 20 years. New targets should be identified, such as hospitalizations and prednisone courses.**

We agree (and acknowledge) that there were large improvements in these outcomes between 1990 and 2005, probably mainly as a result of greater use of inhaled corticosteroids. We chose to focus on the stalling of outcomes after 2005 and took the view that new thinking is required to address this. In commissioning this article, we suspect that the Lancet has come to a similar view. We cannot accept that a disease which still kills young children is a subject for complacency, particularly when such deaths may be readily preventable. We are concerned that outcomes have stalled despite continued increases in spending on treatments. In addition, the clinical community have been slow to embrace new assessment methods despite compelling evidence that they offer the prospect for better diagnosis and stratification. Finally, progress in new drug discovery has been slow and any progress that has occurred has done so because of better stratification as a result of use of these new assessment techniques. Collectively we felt that these issues add considerable impetus to the case for a new approach to the assessment and management of asthma and related airway diseases. We have specifically targeted prednisolone courses and have added to this a recommendation on hospitalisations (see recommendations).

4. **The authors point to the guidelines as a source of complacency in management, however, a number of the panel members have served or currently served on guidelines committees. They know that some guidelines have not been updated for years but GINA provides ongoing updates. The recent emphasis has been to focus on evidence-based principles and frankly some of this evidence is just emerging, the drugs have just been approved, and they are making their way into guidelines. The authors do not make recommendations on what areas should be changed in the guidelines.**

We think this is an excellent point and agree that we need to do more to justify the view that guidelines have become part of the problem. We have added a new section to the second section dealing with this important topic (page 25-26).

5. There is a fair amount of information on predicting treatment response for medications like inhaled corticosteroids, leukotriene antagonist, anticholinergics, but this report places its emphasis on new immunomodulator drugs, that have just been approved or making their way to approval.

We have a paragraph in section 2 calling for more information on predictors of response to leukotriene antagonist and anticholinergics. This has been moved to a new section with a new subheading ('Move from one size fits all management to precision medicine'). The emphasis on immunomodulator drugs is because efficacy was not apparent in unselected populations but became so when a precision medicine strategy was used. We devote a great deal of section 1 and 2 to discussion of the possibility that a similar approach might be applicable with corticosteroid treatment.

6. Some key publications are missing from studies, such as the NHLBI Childhood Asthma Management Program and its long-term observations on pulmonary function (McGeachie et al, NEJM 2016) from childhood to adults. Prior publications from this study identified the element of progression during childhood asthma.

We now reference this important paper (page 38).

7. The summary appears to reflect more of an evolution in knowledge rather than a revolution. In proposing a revolution, the authors do not really propose things that should change, for example, should follow-up spirometry be mandatory in those with respiratory disease or optional as currently practiced? Should all patients with apparent asthma have a set of biomarkers to determine their course of therapy, for example, sputum or blood eosinophils, IgE, exhaled nitric oxide, etc.?

We have revised the summary extensively and have included a new box (box 1) summarising our main recommendations.

8. The authors seem to criticize the pharmaceutical firms for delays in making new drugs available because of regulatory purposes. However, caution is necessary since one of the reasons is to verify safety, especially as one moves to applications in children. Are the authors proposing a fast-track be instituted for moving some impressive drugs forward? That would make sense. It will also be important for investigators to contribute patients to these studies. That is a current problem in moving these drugs forward.

These are key points, which we now emphasise in a revised section 4 (page 48).

9. A meaningful way to move the needle in care is to prompt insurance providers to make changes in the way they reimburse for care. This point is not addressed. Admittedly, they do mention medication adherence as being a problem and perhaps this is another way that insurers could be helpful and clinicians could also be helpful in determining whether the patient really needs daily therapy. Some effort should be made to encourage collaboration.

10. The authors do not really spend a lot of time discussing the cost of the new medications. This has certainly played a role in the limited use and this also needs to be addressed to become more affordable.

We had not considered healthcare payers or insurers but recognise that this was an omission as many of our recommendations are highly relevant to them. We have added short sentences to section 5 (pages 50 and 55) and section 6 (page 57). We have tried not to be too specific as there is wide geographic variability in healthcare systems and we do not want to be too parochial..

11. There are some areas that have not yielded much in terms of care, for example genetics. The authors do not really comment on significant contributions from this area of work that should be included in care or what new biomarkers could be included in clinical care.
We have included a fair amount of genetics in the revised section 7 (epidemiology). We are not convinced that pharmacogenetics has provided clinically useful new insights but recognise it might. We have added a sentence discussing with this possibility to section 1 (page 22).

Reviewer #5: A comprehensive overview of the problems and a new approach to asthma thinking, but at present there are deficits, particularly in weighing up the risks and challenges of the proposed approaches.
MAIN COMMENTS
1. To some extent the problems stated as reasons for the Commission are not answered. Little improvement in asthma outcomes in the last 10 years is attributed to broad and nonspecific labelling and mislabeling, however issues such as the failure to develop and adopt new assessments or the problem of increasing drug treatment costs are not adequately addressed in the paper. Indeed there is a lack of mention of cost effectiveness, and for uncomplicated asthma, wider use of phenotyping may increase costs If these are not really intended to be addressed this sentence should be changed.
We have devoted a large part of section 1 to discussion of new methods of assessment of airway disease. The new text on guidelines addresses the point about failure to take up new assessment techniques. We are not sure that detailed discussion of cost effectiveness of precision medicine is appropriate in a paper that primarily calls for a basic rethink of disease taxonomy and management philosophy. However, we recognise that this will be an important factor as we move forward with this approach and now emphasise that more information on cost effectiveness is needed. We already acknowledge that the sort of precision medicine approach we recommend would not be necessary in mild uncomplicated disease that responds well to low dose ICS.

2. The Executive summary could assist readers to a quick overview of what is being proposed. Key statements or recommendations should be numbered/listed in the Exec Summary (ie the 7 recommendations at the end should appear here). As it is, the Exec summary says more about what was done in the Commission (ie process), not what was recommended (ie outcomes),
This important comment has been addressed (see response to editor's first point).

3. In relation to the structure of the paper, the topics are appropriate but there is some repetition especially in the first 3. In my view the last 3 sections are best written and the first 3 have too much text and are woolly in places.
The first 3 sections have been revised extensively, incorporating sub-headings to better break up the text and make it more accessible.

4. There is a tendency to blame a lot of the shortcomings on the rigidity of labelling and simplistic thinking about "all asthma" as asthma, and not much analysis of other factors. Much of this is reasonable especially the remarks about lack of linkage between physiology and treatment.
Thank you.

5. The section on pages 12-15 is excellent, but there is inadequate analysis of the risks of the proposed approach - of classifying all airways disease under "chronic airways disease" and then sub-grouping, by applying a treatable traits approach. For instance, phenotyping is not well suited to prompt primary care management and may generate costs and unnecessary investigations.

How much more difficult might this approach be? If Test then treat is undertaken, what is done in acute asthma? What would the consequences if non-eosinophilic asthma were not treated with ICS? What RCT evidence supports other treatment approaches for the different non-eosinophilic subgroups? As yet there is no treatable traits trial, so its appeal needs to be countered by an urgent call to undertake these studies.
We devote a large part of section 2 to the risks of the precision medicine approach we advocate, particularly the risks of not treating a patient with non-eosinophilic asthma with ICS. Section 5 suggests that precision medicine could also be applicable in acute asthma. There have been several small and strikingly positive trials of a treatable traits type approach to airway disease. These are discussed already. We do accept that more definitive, clinically directive trials are needed and acknowledge this in section 1 and 2.

6. Overall, although some sections approach it well (eg page 13, (ii)), aspects of primary care management of asthma are touched on too lightly, even though the difficulty of measuring lung function in primary care is mentioned. The response to this must be that we need better tools to do this since persistent AO is sign of poor response to Rx or severe asthma. There is little discussion of the constraints of primary care and the implications of introducing phenotyping as it is not currently undertaken in primary care where most patients are diagnosed, assessed and treated. Additionally, much of the current plateau in sub-optimal outcomes could be attributed to lack of effort and rigour in clinical review, which is hardly mentioned.
We include a section on applying precision medicine in primary care. We suggest that the focus should be on recognition and treatment of the two dominant treatable traits: airflow limitation and eosinophilic airway inflammation. We think that more detailed discussion of the ins and outs of applying this strategy would be outside the scope of this Commission.

7. Your recommendations for non-eosinophilic asthma are not clear. No-one will argue with the idea that people with eosinophilia who fail ICS-LABA should receive anti-IL5 drugs etc; however, what about the significant % partially or poorly controlled patients who are not eosinophilic? One suggested approach is potentially dangerous = no ICS if not eosinophilic. You have not acknowledged the risks of a no-ICS approach while ever there is no RCT evidence to support this. There is some evidence that ICS do help non-eosinophilic disease, but it depends on which endpoints are targeted.
This key point is discussed extensively in section 2. We acknowledge that we cannot be confident about the safety of non-ICS containing treatment regimens in non-eosinophilic asthma and recommend as required ICS/rapid onset beta agonist as the default starting treatment. This will reduce the risks of under treatment in patients who have intermittent eosinophilia.

8. A multidimensional/precision management approach is mainly supported by evidence from studies conducted in tertiary centres (most were not DBRCTs). It should be acknowledged that these trials have not been undertaken in primary care as yet so the implementation of this approach is untested. In particular, the recognition column of Table 4 contains many assessments that are not normally undertaken in primary care.
There is limited evidence from primary care and we call for more. We already suggest that the focus in primary care should be on recognition and treatment of the two dominant treatable traits: airflow limitation and eosinophilic airway inflammation. When these are not present, or morbidity continues despite optimal treatment then assessment for other treatable traits will be needed in specialist care.

9. Mention of the need for cost effectiveness studies should be made - or modelling that enables the costs to be predicted, based on the expected proportion of people who will be treated this

way in the current proposal. Can you give some indication of the % of patients you expect will ideally be treated with monoclonals under your recommendations for precision prescribing?
Around 3% of the total asthma population are suitable for biological treatment. We have added this estimate to the severe asthma section.

10. You refer to the poor asthma outcomes in LMIC's, even with ICS which are relatively cheap - but isn't the main problem here not getting to the people who need ICS? ie poorly applied current recommendations : too infrequently getting to the right lungs?
We acknowledge this in the second section.

10. A key recommendation is on page 26 : the default initial treatment being "as required ICS/SABA or fast onset LABA/ICS, and no escalation of ICS dose unless biomarkers of eosinophilic disease/ICS sub-response are present." This key recommendation needs to appear in the Exec summary with a strong plea for further testing in appropriately designed studies. Could you propose a trial design, to show what you would do in the light of the comments on RCTs?
This has been done. We prefer not to get into the fine details of the sort of RCT required to assess this new approach but are aware that many trials are ongoing.

11. The section on clinical asthma research is excellent on pages 51-58 - especially highlighting current shortcomings in RCT design, possible solutions including innovative statistical approaches, also the need to define asthma more adequately for epidemiologic studies. The current issues facing mouse and animal models are also well covered.
Thank you.

12. Figure 6 concerns me if this is really a treatment proposal; Figure 7 is excellent - very informative; Figures 8-10 haven't downloaded properly, so I can't comment - they appear incomplete
We suspect that the problem with figure 6 is that we have not made it clear enough that: 1) This is a proposal that requires evaluation; and 2) as required ICS/rapid onset beta-agonist is the default reliever option. We have made these points more clearly in the legend. Figures 8-10 have been modified.

We are very grateful for the excellent reviews of the Commission document. We all feel that the document has been improved as a result of this process.

Yours

Ian Pavord
Andy Bush
On behalf of the Commissioners