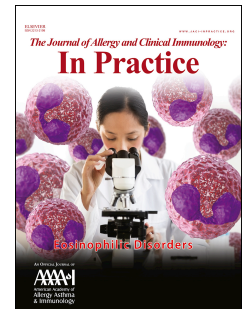


Journal Pre-proof

Towards a Predict and Prevent Approach in Obstructive Airways Diseases

Simon Couillard, MD, MSc, Nayia Petousi, MB BChir, DPhil, Kate S. Smigiel, PhD,
Nestor A. Molfino, MD, MSc



PII: S2213-2198(23)00069-7

DOI: <https://doi.org/10.1016/j.jaip.2023.01.008>

Reference: JAIP 4609

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 5 October 2022

Revised Date: 5 January 2023

Accepted Date: 5 January 2023

Please cite this article as: Couillard S, Petousi N, Smigiel KS, Molfino NA, Towards a Predict and Prevent Approach in Obstructive Airways Diseases, *The Journal of Allergy and Clinical Immunology: In Practice* (2023), doi: <https://doi.org/10.1016/j.jaip.2023.01.008>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

- 1 **Title:** Towards a Predict and Prevent Approach in Obstructive Airways Diseases
- 2 **Authors:** Simon Couillard, MD, MSc¹, Nayia Petousi, MB BChir, DPhil², Kate S. Smigiel, PhD³, Nestor A.
- 3 Molfino, MD, MSc⁴
- 4 ¹Faculté de Médecine et des Sciences de la Santé, Université de Sherbrooke, Sherbrooke, Quebec, Canada;
- 5 ²Respiratory Medicine Unit and NIHR Oxford Respiratory BRC, Nuffield Department of Medicine,
- 6 University of Oxford, Oxford, United Kingdom; ³Global Medical, Amgen Inc., Thousand Oaks, CA, USA;
- 7 ⁴Global Development, Amgen Inc., Thousand Oaks, CA, USA
- 8 **Address for correspondence:** Dr. Nestor A. Molfino, Global Development, Amgen Inc., One Amgen Center
- 9 Drive, Thousand Oaks, CA 91320 (USA). E-mail: nmolfino@amgen.com
- 10 **Descriptor:** Rostrum review article
- 11 **Keywords:** Airway markers, Alarmins, Asthma, Eosinophils, Inflammation, FeNO, Prevention, Prediction,
- 12 Exacerbations, Quality of life
- 13 **Manuscript word count (excluding abstract):** 3490/3500

14 **Financial/nonfinancial disclosures:** The authors declare the following:

- 15 • Funding: This work was supported by the Research Chair of the Association Pulmonaire du
16 Québec, the NIHR Oxford BRC, and Amgen Inc.
- 17 • Role of the sponsor: Amgen provided support for manuscript handling, proofreading, and
18 graphical editing of figures.
- 19 • Ethical approval: Not applicable.
- 20 • Informed consent: Not applicable.
- 21 • Data sharing statement: Not applicable.

22 **Author contributions:** SC, NP, KS, and NM contributed equally to writing and proofreading of the
23 manuscript and guarantee the final content of the manuscript.

24 **Declaration of interests:** SC is supported by Research Chair of the Association Pulmonaire du Québec. He
25 has received non-restricted research grants from Sanofi-Genzyme, the Quebec Respiratory Health
26 Research Network, and the Association Pulmonaire du Québec, outside the submitted work; received
27 speaker honoraria from GlaxoSmithKline, Sanofi-Regeneron and AstraZeneca, outside the submitted
28 work; received reimbursement for conference attendance by AstraZeneca, outside the submitted work;
29 is on the advisory board of Biometry Inc, outside the submitted work. NP is supported from the NIHR
30 Oxford BRC. She has received grants from the University of Oxford and NIHR research capability funding
31 from Oxford University Hospitals outside the submitted work. NM and KS are employees and stockholders
32 of Amgen Inc.

ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are currently diagnosed and treated after demonstration of variable airflow limitation and symptoms. Under this framework, undiagnosed and unchecked airway inflammation is associated with recurrent acute attacks, airway remodeling, airflow limitation, adverse effects of corticosteroids, and impaired quality of life, ultimately leading to the collection of side-effects termed 'people remodeling'. This one-size-fits-all, damage control approach aims to control symptoms and treat exacerbations rather than modify the underlying disease process. The advent of highly effective therapies targeting proximal drivers of airways inflammation calls for a paradigm shift; upstream-acting therapies offer potential to alter the disease course and achieve clinical remission. We propose moving away from downstream firefighting and towards a predict and prevent model, measuring inflammation and providing anti-inflammatory therapy early, without waiting for further clinical deterioration. Much in the same way that high blood pressure and cholesterol are used to predict and prevent heart attacks, in asthma elevated blood eosinophils and/or exhaled nitric oxide (FeNO) can be used to predict and prevent asthma attacks. We advocate also moving research further upstream by identifying patients with subclinical airways inflammation or disease who may be at risk of progressing to airflow limitation and associated morbidities and intervening early to prevent them. In summary, we call for a 'predict and prevent' approach in obstructive airways disease.

50 ABREVIATIONS

51 COPD: chronic obstructive pulmonary disease

52 FeNO: fractional exhaled nitric oxide

53 FEV1: forced expiratory volume in 1 second

54 FVC: forced vital capacity

55 GP: general practitioner

56 ICS: inhaled corticosteroid

57 IL: interleukin

58 OCS: oral corticosteroid

59 T2: type 2

60 TSLP: thymic stromal lymphopoietin

Introduction

Obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), affect 500 million people worldwide and cause significant morbidity and mortality.[1] Healthcare resource utilization for severe asthma is disproportionately high with significant socioeconomic impact,[2] and COPD accounts for 13% of acute hospital admissions.[3] The majority of asthma deaths occur in those with mild-to-moderate disease,[4] and COPD is the third leading cause of adult mortality.[1] Despite increased healthcare expenditure, health outcomes – particularly mortality – have plateaued in the last decade.[5] While reasons for these observations are complex, contributing factors relate to how airways diseases are currently diagnosed, classified, and managed using a “one-size fits all” approach.

I. Why do we need to predict and prevent airways disease?

The current patient journey and trajectory towards established, chronic disease

Obstructive lung diseases are broadly classified as either asthma or COPD. However, there is significant overlap, and within these umbrella terms there is vast heterogeneity in underlying pathophysiology and patient phenotypes. Asthma is often diagnosed in the absence of testing by “trial of treatment”[5] and managed by sequentially increasing the dose of inhaled corticosteroids (ICS) and adding bronchodilators and leukotriene receptor antagonists tailored to symptom control[6, 7] and reduction of exacerbations with biologics.[8] In asthma, the focus on symptom relief may result in suboptimal treatment. For example, patients showing mild disease symptoms but significant risk factors for exacerbation may be undertreated, while those who have been misdiagnosed as asthmatics or who have phenotypes that do not respond well to treatment may suffer medication (and side-effects) overload.[9]

COPD is diagnosed too late in the disease process when post-bronchodilator obstruction becomes apparent on spirometry [ratio of forced expiratory volume in 1 second to the forced vital capacity of the lungs (FEV_1/FVC) <0.7], with severity traditionally graded using $FEV_1\%$ predicted.[6] Treatment similarly includes the stepwise introduction of various bronchodilators and ICS.[6] By the time COPD is diagnosed, significant disease has accumulated unnoticed in the small airways causing irreversible damage.[10, 11] This misses the opportunity for early detection and intervention, particularly in young people who may not yet be functionally limited or symptomatic.

Is there room for prediction and prevention beyond smoking cessation?

Despite smoking being the main risk factor for COPD, only 30% of smokers develop COPD,[12] and there is growing evidence of a non-smoking COPD phenotype in 20-30% of all patients.[13] Furthermore, multiple lung function trajectories can lead to COPD in later life: some people start off with low lung function in early adulthood but have a relatively slow lung function decline, while others progress more rapidly,[14] with the rate of decline being more rapid in earlier disease stages.[15, 16] Indeed, small airways dysfunction occurs early in the disease process, is a precursor of further disease development (e.g., emphysema),[17] and is independently associated with lung function decline.[18]

A study comparing disease trajectories in patients with COPD-alone, asthma-alone, and asthma+COPD identified maternal smoking, childhood respiratory infections before 5 years of age, and family history as more prevalent in those with both asthma and COPD than the other groups.[19] Furthermore, patients with COPD-alone showed rapid lung function decline, while those with asthma+COPD had lower starting lung function in early adulthood but only marginally faster decline than healthy controls.[19] In the Copenhagen City Heart Study, patients with asthma-COPD overlap and early-onset asthma were compared to patients with COPD-alone and to patients with asthma-COPD overlap and late-onset asthma.[20] The latter group showed more rapid lung function decline, increased exacerbation frequency, and reduced life expectancy.[20] While biological reasons may underlie this observation, one possibility is that patients with asthma-COPD overlap and late-onset asthma suffer delayed asthma diagnosis. For these patients, earlier identification and treatment of asthma pathology may be associated with improved prognosis.

This calls for efforts to identify risk factors predictive of the development of future airways disease in early adulthood or late childhood when attainment of maximal lung function occurs. It seems more useful to search for traits that not only put one at risk but that are also modifiable, i.e., “treatable traits”,[21] and aim to predict but also prevent the development of airways diseases and its consequent morbidity.

Can biology help us predict the development of airway disease?

Type 2 (T2) airway inflammation – characterized by T2 cytokine production (e.g., interleukin (IL)-5, IL-4, IL-13) and eosinophilic and allergic inflammation in the presence of atopy – is present in a large proportion

of patients with established airways diseases.[22-24] In both asthma and COPD, T2 inflammation is the most treatment-responsive trait targeted by inhaled and systemic corticosteroids.[24] Asthma can now be treated with biologics targeting inflammatory pathways (anti-IgE, anti-IL-5/5R, anti-IL-4/IL-13, and anti-thymic stromal lymphopoietin (TSLP)),[8] resulting in reduced exacerbation rates. T2 inflammation is easily recognized with clinically accessible biomarkers: fractional exhaled nitric oxide (FeNO) and blood eosinophil count.[25] The combination of these two biomarkers is prognostic of asthma attacks and predictive of treatment response.[26, 27]

There is increasing evidence that the presence of T2 inflammation may predict the development of airways disease. Allergic rhinosinusitis and atopic dermatitis not only coexist with asthma but often precede its development,[28] and the combination of atopic sensitization to aeroallergens with multiple respiratory tract infections in childhood predisposes to subsequent persistent asthma.[29] In a recent large longitudinal cohort study of young healthy individuals, an association was demonstrated between the baseline blood eosinophil count and development of obstructive lung disease with a hazard ratio of 1.3 for blood eosinophils >200 cells/ μ L and an almost 2-fold risk in those with blood eosinophils >500 cells/ μ L, compared to <100 cells/ μ L, in both smokers and non-smokers.[30] In additional studies, blood eosinophils correlated with lung function decline even in healthy individuals without asthma,[31, 32] and a 3-fold increase in baseline blood eosinophils was associated with an increase in the rate of FEV₁ decline equivalent to that seen with a 10 pack-year history.[32] FeNO has also been associated with lung function decline in asthma,[33, 34] although this association has not been tested in health.

II. A proposed framework to predict and prevent in airways disease

From downstream firefighters to upstream predict-and-preventors

In view of the substantial body of knowledge recently gained to predict and prevent airways-related morbidity,[5, 27, 35] there is an opportunity to move past 'downstream firefighting' and become 'predict-and-preventors' (**Figure 1**).

Current model: the firefighter approach

In mild-to-moderate airways disease, general practitioners (GPs), or “firefighters”, routinely assess risk factors for airflow obstruction (e.g., environmental exposures and smoking) and recommend measures to mitigate the risk of acute or chronic airflow deterioration. For example, they prescribe bronchodilators and/or higher-dose ICS according to a predefined treatment ladder largely based on symptomatic disease control, i.e., reacting when symptoms or airflow deteriorates.[7, 36, 37] This delayed approach in airways disease, which waits for recurrent exacerbations when treatment-responsive biology is present, is at odds with the GP’s actions in cardiovascular disease, where blood pressure, serum cholesterol, and functional capacity as well as imaging tests guide therapeutic decision-making before deleterious health outcomes occur.[38] This is also in contrast to the approach taken by GPs predicting and preventing osteoporosis, where a biomarker (bone mineral density) is used to identify patients at risk of a specific outcome (fracture), and treatment is started to prevent this outcome. In an increasing number of patients, this preventive, biomarker-driven treatment is accomplished with a biologic.[39]

While some progress has been made in asthma and COPD guidelines, where the peripheral blood eosinophil count can guide the initiation of ICS in COPD [6] and biologics in asthma,[7] national guidelines do not always endorse this approach.[37] This results in lack of awareness on the utility of T2 biomarkers such as blood eosinophils and/or FeNO to target increased airways inflammation.[40] If left untreated, airways inflammation can provoke acute attacks requiring prescription of systemic corticosteroids and/or antibiotics to provide relief, with the unfortunate consequence of adverse events.[41-44] Progress has also been made with use of the combination of ICS and a long-acting bronchodilator for both maintenance and quick relief therapy, which has been shown to reduce severe exacerbations and cumulative steroid exposure.[45] The hypothesis that the success of this approach is related to the early treatment of T2 inflammation that is increased prior to a period of loss of control[46] is still under investigation.[47]

When disease remains uncontrolled, a proportion of patients will be referred to the respirologist-firefighter. If the diagnosis is indeed asthma, specialists assume that most ($\geq 50\%$) of severe disease is caused by smouldering T2 eosinophilic airway inflammation.[48] High-dose ICS are prescribed first, and for some patients, oral corticosteroids (OCS) are necessary.[49-53] Indeed, OCS are helpful when airway mucosal mechanisms drive recruitment of eosinophils towards the airway epithelium because they may

deplete the reservoir of circulating eosinophils,[54] thus preventing eosinophil recruitment even in the presence of a strong chemotactic pull towards the airway epithelium.[53, 55] More recently, the availability of monoclonal antibodies to treat patients with severe asthma has translated to extraordinary efficacy in both 'red-hot' inflammatory asthma, defined as asthma with elevated levels of blood eosinophils and FeNO, as well as in patients with less evidence of T2 inflammation.[8, 56] At last, the specialist-firefighter addresses the scarred and scared severe asthmatic's problem with a targeted biologic.

Thus, from start to end of the asthmatic's experience under the firefighter approach, recurrent attacks can lead to irreversible airflow limitation, lung function decline, and airway remodelling.[57, 58] While systemic corticosteroids may treat the inflammation causing the clinical problem, their combination with uncontrolled airway disease reshapes the appearance, health status, and life of patients.[41, 42, 44, 59] Similar to airway remodelling, involving loss of airway lumen and function due to recurrent asthma attacks, the impairment in quality of life due to the impacts of uncontrolled airway disease and physiognomic changes due to the adverse effects of systemic corticosteroids can lead to what is referred to as "people remodelling". With the downstream-firefighter approach, the processes of airway and people remodelling are progressive and universal because the treatments are not tailored to the patients' airway biology or biomarkers until the very last stage of the disease, at which point they have suffered irreversible damage (**Figure 1A**).

The predict-and-preventors

The predict-and-preventor's tasks involve early phenotyping of patients clinically (by looking for treatable comorbidities) and objectively (by measuring T2 inflammatory biomarkers and lung function) to decipher the underlying mechanisms of their airway disease,[60] estimate the risk of asthma attacks,[35] predict lung function decline,[30, 32, 34, 61] and most importantly, choose the right treatment for the right patient before airway and people remodeling occur.[5, 27, 62]

This approach is based on recent analyses of the control arms of randomized clinical trials and real-world cohorts across the range of asthma severities showing that the baseline combination of blood eosinophil count and FeNO level identifies patients at risk of future asthma attacks,[26, 35, 63-68] and lung function

decline.[32, 34, 61] Similar relationships have been observed at all stages of COPD for acute attacks[40, 69-74] and lung function decline.[30] This relationship between baseline blood eosinophils, FeNO, and deleterious outcomes appears to be similar in strength and additive to that seen with other risk factors such as a history of an attack in the last year and treatment step.[75, 76] Importantly, the excess risk associated with elevated T2 biomarkers can be reduced with ICS in mild asthma[77] or COPD, higher-dose ICS in moderate asthma,[66, 67] and biologics targeting T2 inflammation in severe asthma.[78-83] Collectively, these findings suggest that, in T2 asthmatics, blood eosinophils and FeNO are important prognostic and theragnostic biomarkers across the range of airways disease severities.[35] Admittingly, these conclusions are mostly based on *post-hoc* analyses and, in consequence, the derivation and validation of a robust clinical prediction model centered on blood eosinophils and FeNO in people with asthma is under investigation.[84] Whether the use of biomarkers in patients with established airways diseases supports extrapolation of these biomarkers as predictors of early disease or disease onset is not entirely known and requires further study.

The predict-and-preventor identifies patients with inflamed (T2) airways, who are at risk of airway and people remodeling and act upstream to avoid predictable and avoidable downstream firefighting. (**Figure 1B**)

III. Pathomorphosis of airways disease: the influence of novel therapeutics and environment on the treatment paradigm

Because of environmental changes and the introduction of new therapeutic approaches, we are witnessing several changes – a pathomorphosis – in what we call airways disease.[85] Pathomorphosis is defined as the changes in clinical disease presentation that occur under the influence of various factors, including genetic and environmental changes, new treatments, and owing to lung ontogenic evolution.[86] Throughout history there have been examples of medicine altering the trajectory of disease: in World War I, the hypovolemic shock resulting from major trauma and blood loss led to the use of rudimentary blood transfusion, which led to acute renal failure. This brought about dialysis, which increased the incidence of acute respiratory distress syndrome (ARDS), which in turn led to improved methods of life-saving mechanical ventilation. Prolonging life through mechanical ventilation has led to ventilator-associated pneumonia and septic shock. Thus, through therapeutic interventions, shock has

morphed from hypovolemic to septic. Asthma and COPD are undergoing comparable modifications from purely bronchoconstrictive conditions to modifiable inflammatory ones.

The advent of biologics targeting inflammatory pathways in asthma

Although asthma was first described several centuries ago,[87] specific phenotype-designed therapeutic approaches have only been developed in the last two decades. This may be the result of using a general umbrella diagnosis for a syndrome that consists of different –sometimes overlapping – traits. Asthma was initially considered a purely bronchospastic disorder, and it was only in the mid-1990s that airways inflammation was demonstrated even in mild asymptomatic asthmatics.[88] More recently, different types of airways inflammation have become apparent, notably the continuum ranging from T2 low to T2 high.[89, 90] Of note, this continuum is dynamic, with nearly 1 in 2 patients with severe asthma assigned to a different biomarker cluster after 1 year of follow-up.[91]

If left untreated, the natural history of asthma ranges from mild symptoms to life-threatening or even death.[92] Asthma can go into clinical remission for periods of time and even indefinitely.[93] In this regard, mild asthma does not necessarily mean low-risk asthma, and it is now time to start thinking of treating the inflammation signature to avert further deterioration of the disease.

Over the years asthma has been treated with bronchodilators, xanthines, leukotriene modifiers, corticosteroids, immunosuppressants, and now biologics.[94] Each type of asthma treatment can provoke different levels of benefits and pathophysiological changes in the airways. In severe asthma, targeted therapy with biologics has increased our understanding of how blocking specific immune pathways (e.g., IgE, IL-4/13, IL-5, and TSLP) influences clinical outcomes and may modify its natural course. With such therapeutic armamentarium and increased knowledge on biomarkers, we are now able to assess the prognosis of individuals with asthma, predict the clinical response to treatment, and avert further deterioration of lung function as well as reduce the risk of exacerbations and hospitalizations.[95]

This is certainly doable now in T2-high asthma where reduction of the risk of exacerbations and hospitalizations and induction of clinical remission may be possible in a biomarker-directed fashion.[96] Although work is needed to identify and treat T2-low asthmatics, who in general exhibit several other comorbidities (i.e., COPD and obesity), new therapies are emerging.[97, 98] There are now therapies

available that target T2-high asthma, therapies that target T2-low asthma, and therapies that can treat both phenotypes by targeting the epithelium (**Table 1**). Conversely, the lack of currently available and effective biologic treatments for COPD leaves an unmet need for effective therapeutics to treat COPD. However, by targeting within the COPD group those patients with T2 inflammation and co-existence of asthmatic features, we may be able to target the right therapeutic to the right disease phenotype by targeting treatable traits irrespective of the diagnostic label.

Understanding the environmental and social determinants of airways disease

Environmental factors such as infection, pollution, allergens, climate change, and housing conditions are known to contribute to both the initial onset and exacerbation of airways disease,[99] and greater understanding – and hopefully mitigation – of these environmental insults on the asthma landscape will inform next-generation treatment paradigms. In tandem with a patient’s genetic predisposition, asthma can evolve into several phenotypes owing to *in utero* exposures,[100, 101] factors in the environment that trigger immune responses and inflammation in the airways,[102] personalized targeted therapies,[95] and climate change.[103, 104] The latter affects air quality and likely plays a role in the displacement of vectors that provoke respiratory infections that can influence the epidemiology of asthma.[90]

Environmental factors often synergize with social determinants of health (e.g., economic stability, access to healthcare and education, and health literacy) to disproportionately skew the burden of asthma morbidity and mortality towards underrepresented groups, particularly Black and Latinx patients.[105] To address the goal of health equity for all, current and future therapeutics should be evaluated in clinical trials with racially and ethnically diverse populations,[106] and those trials need to collect better data on participants’ socioeconomic status, level of education, insurance coverage, and other social determinants of health to ensure that the information used for creation of national guidelines is generalizable to all patients.[107]

Raising the bar for effective therapies: achieving clinical remission and withdrawal of OCS

The bar for demonstrating effective treatment of severe asthma has been raised, with new therapeutic targets focused on disease modification and clinical remission. The ambition to achieve a stable period

with little to no disease activity, optimized lung function, and lack of systemic steroid treatment – termed clinical remission – has now become a therapeutic target with the advent of biologic therapies.[96, 108]

The campaign for remission in asthma is supported by outstanding progress in rheumatology, where clinicians treating rheumatoid arthritis with disease-modifying antirheumatic drugs and biologics have advanced the treatment paradigm to long-term complete control with less disease progression.[109] In asthma, severe exacerbations with associated bursts of OCS and hospital care contribute to a self-perpetuating cycle of epithelial damage, inflammation, tissue remodeling, and impaired lung function.[57, 110] Biologics are effective OCS-sparing agents, particularly in patients with eosinophilic asthma, and increasing use of biologics has made tapering and cessation of maintenance OCS more common and feasible. A recent consensus study found that 95% of experts agree the goal should be to avoid OCS completely, yet long-term OCS therapy is estimated to be used in 20-60% of severe asthma patients.[111] Even in mild asthma, as few as 4-5 lifetime OCS courses increases the risk of osteoporosis, diabetes, and cataract,[112] and long-term OCS use is associated with increased mortality, reduced quality of life, and increased healthcare resource utilization and costs.[59]

Thus, further research is needed to substantiate clinical guidelines aimed at tapering or replacing OCS with safer management options. Ongoing clinical trials will aim to assess whether available biologic therapies can modify the natural history of moderate-to-severe asthma, through reductions in airway hyperresponsiveness and remodeling and prevention of lung function decline. The development and evaluation of new biologic therapies combining symptom control with disease modification will likely be needed to establish clinical remission as a realistic treatment goal. Yet more work is needed in mild asthma. In children, predicting the development of asthma has been attempted using different clinical indices methods,[113] and more recently algorithms and machine learning have been identified as a tool to predict asthma development.[27, 114] The treatment paradigm for childhood asthma has begun to shift towards earlier intervention, as control of inflammation early in life may help to preserve lung function in adulthood, although there is a paucity of data in children under 5 years of age.[115] The goal should be to diagnose early predisposition in healthy individuals using biomarkers as well as polygenic risk scores, at which time patients can be advised of risks and make therapeutic or preventive decisions.

Conclusion

In summary, with the availability and validation of accessible biomarkers, it is now possible to determine if T2 airway inflammation – a treatable trait – is present in all patients with asthma and COPD, even in asymptomatic individuals. The first step in the way forward is to implement a predict and prevent approach in those diagnosed with airways disease early in their patient journey. For the busy clinician, the message is to phenotype early in the patient's disease and direct treatment to treatable processes rather than just relying on symptoms. Indeed, appropriate biomarker-based phenotyping can identify high-risk disease, defined as multiple exacerbations or accelerated lung function decline, and effectively target the right therapy to the right patient at the right time. The aim here should be to achieve clinical remission and prevent further airway and people remodeling. We advocate for research to move the predict and prevent approach further upstream in the disease process, identifying T2 airways inflammation early – even in the subclinical state, as this may pose significant risk of developing future airflow limitation and morbidity – and intervening to prevent it. For this to be realized, what is required is to combine accessible biomarkers (i.e., blood eosinophils, FeNO) with new, sensitive physiological measures that can detect subtle or early changes in the small airways,[116] in order to identify those in whom intervention may be more impactful.

321 **Table 1. Currently available treatments that avert asthma exacerbations in severe asthmatics.**

T2 HIGH ^[7, 117, 118]	T2 LOW ^[66, 119, 120]
Corticosteroids Long-acting beta-2 agonists Macrolides (in the presence of infection) Mepolizumab Reslizumab Benralizumab Omalizumab Dupilumab Tezepelumab	Long-acting beta-2 agonists Antimuscarinics (for airway obstruction) Macrolides Tezepelumab

322

Figure Legends

Figure 1A. ‘Downstream firefighting’ of airway disease involves prescribing inhaled therapy and systemic corticosteroids at times of loss of control to alleviate symptoms and acute airway attacks. Because the underlying incendiary process of type 2 inflammation remains active, this one-size-fits-all downstream approach is associated with airway remodelling (e.g., loss of airway lumen and function due to recurrent airway attacks – especially in inflamed, ‘red hot’ airways, identified by elevated type 2 biomarkers) and people remodelling (e.g., impairment in quality of life due to the impacts of uncontrolled airway disease and physiognomic changes due to the adverse effects of corticosteroids). With the firefighter approach, the process of airway/people remodelling is universal because our treatments are not tailored to the patients’ airway biology and biomarkers until the very last stage of the disease, at which point they have suffered irreversible damage.

Figure 1B. An upstream ‘predict and prevent’ approach could avoid substantial airway/people remodelling by identifying and tackling underlying causal pathways that may lead to the development of airway disease, uncontrolled symptoms, loss of lung function, and recurrent attacks. Predict-and-preventors measure biomarkers with mechanistic, prognostic, and theranostic values such as the blood/sputum eosinophil (eos) count and fractional exhaled nitric oxide (FeNO) to pulverize the problem at its source. We speculate that measuring biomarkers early can lead to faster identification of ‘hot-but-well’ people with high-risk airways. The potential impact of targeting modifiable risk at all stages of disease would be to avoid substantial airway/people remodelling in airway disease – a pathomorphosis.

References

1. European Respiratory Society, on behalf of the Forum of International Respiratory Societies (FIRS). The Global Impact of Respiratory Disease – Second Edition. 2017.
2. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax*. 2015;70(4):376-78.
3. Andersson F, Borg S, Jansson SA, Jonsson AC, Ericsson A, Prütz C, et al. The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med*. 2002;96(9):700-08.
4. Levy ML, Winter R. Asthma deaths: What now? *Thorax*. 2015;70(3):209-10.
5. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: Redefining airways diseases. *Lancet*. 2018;391(10118):350-400.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD (2022 Report). 2022.
7. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (Updated 2022). 2022.
8. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386(2):157-71.
9. Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe (Sheff)*. 2019;15(1):e20-e7.
10. Burgel PR. The role of small airways in obstructive airway diseases. *Eur Respir Rev*. 2011;20(119):23-33.
11. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-53.
12. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med*. 2009;180(1):3-10.
13. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. COPD in never smokers: Results from the population-based burden of obstructive lung disease study. *Chest*. 2011;139(4):752-63.
14. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373(2):111-22.
15. Tantucci C, Modina D. Lung function decline in COPD. *Int J Chron Obstruct Pulmon Dis*. 2012;7:95-99.
16. Drummond MB, Hansel NN, Connett JE, Scanlon PD, Tashkin DP, Wise RA. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;185(12):1301-06.
17. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365(17):1567-75.
18. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2016;194(2):178-84.
19. Marcon A, Locatelli F, Dharmage SC, Svanes C, Heinrich J, Leynaert B, et al. The coexistence of asthma and COPD: Risk factors, clinical history and lung function trajectories. *Eur Respir J*. 2021;58(5).

20. Lange P, Çolak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: A prospective population-based analysis. *Lancet Respir Med*. 2016;4(6):454-62.
21. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: Toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47(2):410-19.
22. Fahy JV. Type 2 inflammation in asthma – present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65.
23. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180(5):388-95.
24. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: Prevalence and clinical characteristics. *Eur Respir J*. 2014;44(6):1697-700.
25. Kim MA, Shin YS, Pham le D, Park HS. Adult asthma biomarkers. *Curr Opin Allergy Clin Immunol*. 2014;14(1):49-54.
26. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: A post hoc analysis. *Am J Respir Crit Care Med*. 2019;200(10):1308-12.
27. Couillard S, Do WH, Beasley R, Hinks TSC, Pavord ID. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE). *ERJ Open Res*. 2022;8(1).
28. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol*. 2000;106(5 Suppl):S201-05.
29. Kusel MM, de Klerk NH, Kebabdz T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*. 2007;119(5):1105-10.
30. Park HY, Chang Y, Kang D, Hong YS, Zhao D, Ahn J, et al. Blood eosinophil counts and the development of obstructive lung disease: The Kangbuk Samsung Health Study. *Eur Respir J*. 2021;58(4).
31. Lee SH, Ahn KM, Lee SY, Kim SS, Park HW. Blood eosinophil count as a predictor of lung function decline in healthy individuals. *J Allergy Clin Immunol Pract*. 2021;9(1):394-9.e1.
32. Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. *Eur Respir J*. 2018;51(4).
33. Nerpin E, Ferreira DS, Weyler J, Schlunssen V, Jogi R, Raheison Semjen C, et al. Bronchodilator response and lung function decline: Associations with exhaled nitric oxide with regard to sex and smoking status. *World Allergy Organ J*. 2021;14(5):100544.
34. Pavord ID, Brusselle G, Jackson DJ, Brightling CEE, Papi A, Maspero JF, et al. FeNO as a potential prognostic and predictive marker of lung function decline in patients with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA QUEST. B93 *Breakthroughs In Pediatric And Adult Asthma Clinical Trials*. 2022. pA3418-A.
35. Couillard S, Laugerud A, Jabeen M, Ramakrishnan S, Melhorn J, Hinks T, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax*. 2022;77(2):199-202.
36. Yang CL, Hicks EA, Mitchell P, Reisman J, Podgers D, Hayward KM, et al. Canadian Thoracic Society 2021 guideline update: Diagnosis and management of asthma in preschoolers, children and adults. *Can J Respir Crit Care Sleep Med*. 2021;5(6):348-61.

37. Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;201(9):e56-e69.
38. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987-1003.
39. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33(10):2049-102.
40. Singh D, Agusti A, Martinez FJ, Papi A, Pavord ID, Wedzicha JA, et al. Blood eosinophils and chronic obstructive pulmonary disease: A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review. *Am J Respir Crit Care Med*. 2022;206(1):17-24.
41. Blakey J, Chung LP, McDonald VM, Ruane L, Gornall J, Barton C, et al. Oral corticosteroids stewardship for asthma in adults and adolescents: A position paper from the Thoracic Society of Australia and New Zealand. *Respirology*. 2021;26(12):1112-30.
42. Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: Striking the balance between efficacy and safety. *Eur Respir Rev*. 2020;29(155).
43. Ramakrishnan S, Couillard S. Antibiotics for asthma attacks: Masking uncertainty. *Eur Respir J*. 2021;58(1).
44. Bleeker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med*. 2020;201(3):276-93.
45. Reddel HK, Bateman ED, Schatz M, Krishnan JA, Cloutier MM. A practical guide to implementing SMART in asthma management. *J Allergy Clin Immunol Pract*. 2022;10(1s):S31-S38.
46. Psallidas I, Backer V, Kuna P, Palmér R, Necander S, Aurell M, et al. A Phase 2a, double-blind, placebo-controlled randomized trial of inhaled TLR9 agonist AZD1419 in asthma. *Am J Respir Crit Care Med*. 2021;203(3):296-306.
47. Harrison T, Pavord ID, Chalmers JD, Whelan G, Fagerås M, Rutgersson A, et al. Variability in airway inflammation, symptoms, lung function and reliever use in asthma: Anti-inflammatory reliever hypothesis and STIFLE study design. *ERJ Open Res*. 2020;6(2).
48. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med*. 2021;9(1):57-68.
49. Pavord ID, Brightling CEE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet*. 1999;353(9171):2213-14.
50. Medical Research Council (MRC). Controlled trial of effects of cortisone acetate in status asthmaticus: Report to the Medical Research Council by the subcommittee on clinical trials in asthma. *Lancet*. 1956;268(6947):803-06.
51. Berry M, Morgan A, Shaw DE, Parker D, Green R, Brightling C, et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax*. 2007;62(12):1043-49.
52. Couillard S, Shrimanker R, Lemaire-Paquette S, Hynes GM, Borg C, Connolly C, et al. Longitudinal changes in sputum and blood inflammatory mediators during FeNO suppression testing. *Thorax*. 2022;77:933-938.

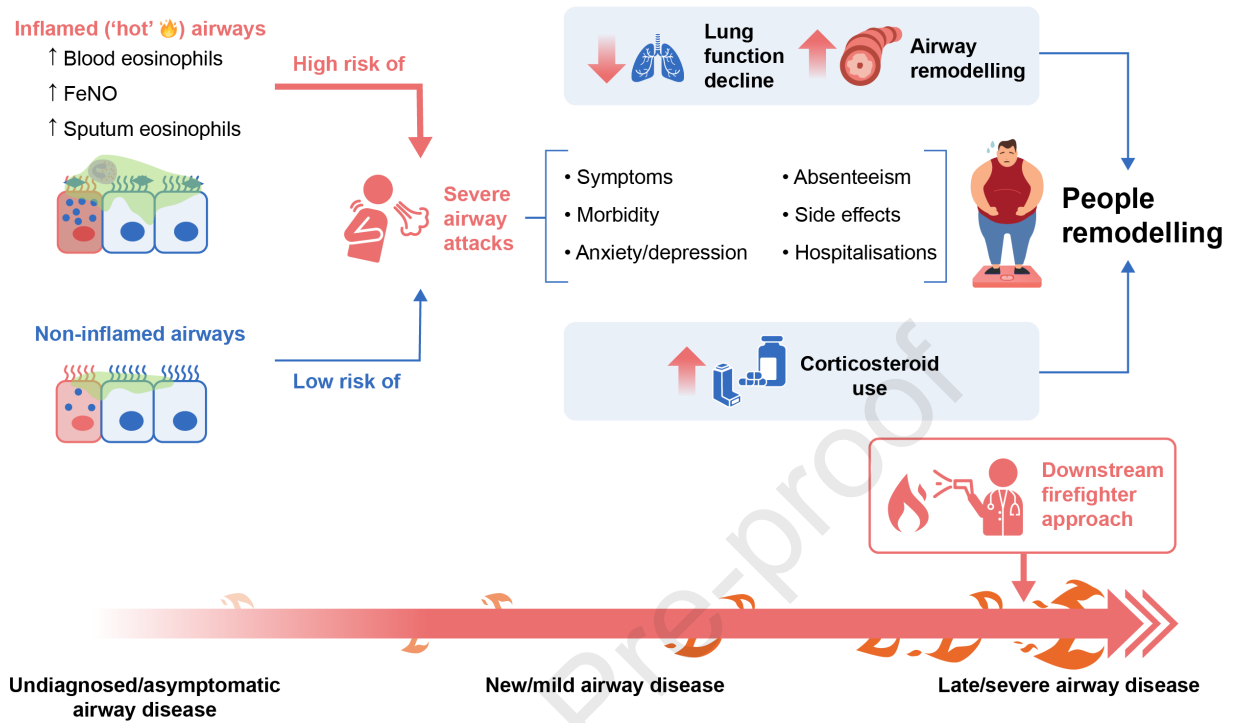
53. Couillard S, Shrimanker R, Chaudhuri R, Mansur AH, McGarvey LP, Heaney LG, et al. Fractional exhaled nitric oxide nonsuppression identifies corticosteroid-resistant type-2 signaling in severe asthma. *Am J Respir Crit Care Med*. 2021;204(6):731-34.
54. Thorn GW, Renold AE, Wilson DL, Frawley TF, Jenkins D, Garcia-Reyes J, et al. Clinical studies on the activity of orally administered cortisone. *N Engl J Med*. 1951;245(15):549-55.
55. Couillard S, Pavord ID, Heaney LG, Petousi N, Hinks TSC. Sub-stratification of type-2 high airway disease for therapeutic decision-making: A 'bomb' (blood eosinophils) meets 'magnet' (FeNO) framework. *Respirology*. 2022;27(8):573-77.
56. Couillard S, Pavord ID. Biological therapies for asthma. *Encyclopedia of Respiratory Medicine*. Edited by Janes S, 2nd Edition, Elsevier. 2021:411-34.
57. Matsunaga K, Hirano T, Oka A, Tanaka A, Kanai K, Kikuchi T, et al. Progression of irreversible airflow limitation in asthma: Correlation with severe exacerbations. *J Allergy Clin Immunol Pract*. 2015;3(5):759-64.e1.
58. Soremekun S, Heaney LG, Skinner D, Bulathsinhala L, Carter V, Chaudhry I, et al. Asthma exacerbations are associated with a decline in lung function: A longitudinal population-based study. *Thorax*. 2022. [published online ahead of print]
59. Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegård A, Davidsen JR. Low dose oral corticosteroids in asthma associates with increased morbidity and mortality. *Eur Respir J*. 2022;60(3):2103054
60. Couillard S, Jackson D, Wechsler M, Pavord I. How I do it: workup of severe asthma. *Chest*. 2021;160(6):2019-29.
61. Coumou H, Westerhof GA, de Nijs SB, Zwinderman AH, Bel EH. Predictors of accelerated decline in lung function in adult-onset asthma. *Eur Respir J*. 2018;51(2).
62. Petousi N, Wooden A, Russell REK. A new piece in the puzzle: The eosinophil and the development of COPD. *Eur Respir J*. 2021;58(4).
63. Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: A prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med*. 2020;8(7):671-80.
64. Busse WW, Wenzel SE, Casale TB, FitzGerald JM, Rice MS, Daizadeh N, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: A post-hoc analysis. *Lancet Respir Med*. 2021;9(10):1165-73.
65. Kraft M, Brusselle G, FitzGerald JM, Pavord ID, Keith M, Fagerås M, et al. Patient characteristics, biomarkers and exacerbation risk in severe, uncontrolled asthma. *Eur Respir J*. 2021;58(6).
66. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): A double-blind, randomised, phase 3A trial. *Lancet Respir Med*. 2021;9(1):69-84.
67. Couillard S, Pavord ID. Fluticasone furoate: CAPTAIN of fluticasones in type-2 inflammatory asthma. *Respirology*. 2022;27(3):184-86.
68. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: A UK cohort study. *Lancet Respir Med*. 2015;3(11):849-58.
69. Bélanger M, Couillard S, Courteau J, Larivée P, Poder TG, Carrier N, et al. Eosinophil counts in first COPD hospitalizations: A comparison of health service utilization. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3045-54.

70. Couillard S, Larivée P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. *Chest*. 2017;151(2):366-73.
71. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48.
72. Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: Analysis of the IMPACT trial. *Lancet Respir Med*. 2019;7(9):745-56.
73. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378(18):1671-80.
74. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: Just another biomarker? *Lancet Respir Med*. 2017;5(9):747-59.
75. Adibi A, Sin DD, Safari A, Johnson KM, Aaron SD, FitzGerald JM, et al. The acute COPD exacerbation prediction tool (ACCEPT): A modelling study. *Lancet Respir Med*. 2020;8(10):1013-21.
76. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulm Med*. 2017;17(1):74.
77. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med*. 2019;380(21):2020-30.
78. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-59.
79. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: A phase 2b randomised dose-ranging study. *Lancet Respir Med*. 2014;2(11):879-90.
80. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-96.
81. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-46.
82. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800-09.
83. FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: Pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6(1):51-64.
84. Couillard S, Steyerberg E, Beasley R, Pavord I. Blood eosinophils, fractional exhaled nitric oxide and the risk of asthma attacks in randomised controlled trials: Protocol for a systemic review and control arm patient-level meta-analysis for clinical prediction modelling. *BMJ Open*. 2022;12(4):e058215.
85. Tang HHF, Teo SM, Sly PD, Holt PG, Inouye M. The intersect of genetics, environment, and microbiota in asthma-perspectives and challenges. *J Allergy Clin Immunol*. 2021;147(3):781-93.
86. Molino NA. Evolución funcional del pulmón y síntomas respiratorios. *Archivos de Bronconeumología*. 2004;40(10):429-30.
87. Marketos SG, Ballas CN. Bronchial asthma in the medical literature of Greek antiquity. *J Asthma*. 1982;19(4):263-9.
88. Chu EK, Drazen JM. Asthma. *Am J Respir Crit Care Med*. 2005;171(11):1202-08.
89. Tay HL, Foster PS. Biologics or immunotherapeutics for asthma? *Pharmacol Res*. 2020;158:104782.

- 565 90. Murphy RC, Pavord ID, Alam R, Altman MC. Management strategies to reduce exacerbations in
566 non-T2 asthma. *J Allergy Clin Immunol Pract.* 2021;9(7):2588-97.
- 567 91. Kupczyk M, Dahlén B, Sterk PJ, Nizankowska-Mogilnicka E, Papi A, Bel EH, et al. Stability of
568 phenotypes defined by physiological variables and biomarkers in adults with asthma. *Allergy.*
569 2014;69(9):1198-204.
- 570 92. Molfino NA, Nannini LJ, Martelli AN, Slutsky AS. Respiratory arrest in near-fatal asthma. *N Engl J*
571 *Med.* 1991;324(5):285-88.
- 572 93. Koefoed HJL, Vonk JM, Koppelman GH. Predicting the course of asthma from childhood until early
573 adulthood. *Curr Opin Allergy Clin Immunol.* 2022;22(2):115-22.
- 574 94. von Mutius E, Drazen JM. A patient with asthma seeks medical advice in 1828, 1928, and 2012. *N*
575 *Engl J Med.* 2012;366(9):827-34.
- 576 95. Melhorn J, Howell I, Pavord ID. Should we apply a treatable traits approach to asthma care? *Ann*
577 *Allergy Asthma Immunol.* 2022;128(4):390-97.
- 578 96. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert
579 consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol.* 2020;145(3):757-
580 65.
- 581 97. Niessen NM, Fricker M, McDonald VM, Gibson PG. T2-low: What do we know?: Past, present, and
582 future of biologic therapies in noneosinophilic asthma. *Ann Allergy Asthma Immunol.* 2022;129(2):150-
583 59.
- 584 98. Ebina-Shibuya R, Leonard WJ. Role of thymic stromal lymphopoietin in allergy and beyond. *Nat*
585 *Rev Immunol.* 2022;1-14.
- 586 99. Thurston GD, Balmes JR, Garcia E, Gilliland FD, Rice MB, Schikowski T, et al. Outdoor air pollution
587 and new-onset airway disease. An official American Thoracic Society Workshop Report. *Ann Am Thorac*
588 *Soc.* 2020;17(4):387-98.
- 589 100. Gao Y, Nanan R, Macia L, Tan J, Sominsky L, Quinn TP, et al. The maternal gut microbiome during
590 pregnancy and offspring allergy and asthma. *J Allergy Clin Immunol.* 2021;148(3):669-78.
- 591 101. Murphy VE, Karmaus W, Mattes J, Brew BK, Collison A, Holliday E, et al. Exposure to stress and air
592 pollution from bushfires during pregnancy: Could epigenetic changes explain effects on the offspring? *Int*
593 *J Environ Res Public Health.* 2021;18(14).
- 594 102. Bhakta NR, Woodruff PG. Human asthma phenotypes: From the clinic, to cytokines, and back
595 again. *Immunol Rev.* 2011;242(1):220-32.
- 596 103. Agache I, Sampath V, Aguilera J, Akdis CA, Akdis M, Barry M, et al. Climate change and global
597 health: A call to more research and more action. *Allergy.* 2022;77(5):1389-407.
- 598 104. Pacheco SE, Guidos-Fogelbach G, Annesi-Maesano I, Pawankar R, G DA, Latour-Staffeld P, et al.
599 Climate change and global issues in allergy and immunology. *J Allergy Clin Immunol.* 2021;148(6):1366-
600 77.
- 601 105. Leong AB, Ramsey CD, Celedón JC. The challenge of asthma in minority populations. *Clin Rev*
602 *Allergy Immunol.* 2012;43(1-2):156-83.
- 603 106. González Burchard E, Borrell LN. Need for racial and ethnic diversity in asthma precision medicine.
604 *N Engl J Med.* 2021;385(24):2297-98.
- 605 107. Bryant-Stephens T. Breaking the skin color barriers for asthma medications – It's not Black, Brown,
606 or White. *N Engl J Med.* 2022;386(16):1574-75.
- 607 108. Porsbjerg C, Maitland-van der Zee AH, Brusselle G, Canonica GW, Agusti A, Faner R, et al. 3TR: A
608 pan-European cross-disease research consortium aimed at improving personalised biological treatment
609 of asthma and COPD. *Eur Respir J.* 2021;58(4).

109. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis*. 2011;70(3):404-13.
110. Dougherty RH, Fahy JV. Acute exacerbations of asthma: Epidemiology, biology and the exacerbation-prone phenotype. *Clin Exp Allergy*. 2009;39(2):193-202.
111. Suehs CM, Menzies-Gow A, Price D, Bleecker ER, Canonica GW, Gurnell M, et al. Expert consensus on the tapering of oral corticosteroids for the treatment of asthma. A Delphi study. *Am J Respir Crit Care Med*. 2021;203(7):871-81.
112. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: Long-term observational study. *J Asthma Allergy*. 2018;11:193-204.
113. Castro-Rodriguez JA, Cifuentes L, Martinez FD. Predicting asthma using clinical indexes. *Front Pediatr*. 2019;7:320.
114. Jiao T, Schnitzer ME, Forget A, Blais L. Identifying asthma patients at high risk of exacerbation in a routine visit: A machine learning model. *Respir Med*. 2022;198:106866.
115. Szeffler SJ. Asthma across the lifespan: Time for a paradigm shift. *J Allergy Clin Immunol*. 2018;142(3):773-80.
116. Petousi N, Talbot NP, Pavord I, Robbins PA. Measuring lung function in airways diseases: Current and emerging techniques. *Thorax*. 2019;74(8):797-805.
117. Chheang C, Guinand S, von Garnier C, Sartori C. New perspectives of biological therapy for severe asthma in adults and adolescents. *Swiss Med Wkly*. 2022;152:w30176.
118. Parnes JR, Molfino NA, Colice G, Martin U, Corren J, Menzies-Gow A. Targeting TSLP in asthma. *J Asthma Allergy*. 2022;15:749-65.
119. Ricciardolo FLM, Carriero V, Bertolini F. Which therapy for non-type(T)2/T2-low asthma. *J Pers Med*. 2021;12(1).
120. Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. *N Engl J Med*. 2019;380(21):2009-19.

A. Downstream firefighting is associated with greater airway remodelling and people remodelling



B. Upstream predict-and-prevent approach avoids substantial airway and people remodelling

