# Asthma Update 2023

## Part 1: Modern Asthma Management

Asthma is a major serious global health problem, affecting both children and adults. More than 260 million people worldwide were affected by asthma in 2019. Asthma is a chronic inflammatory disease of the airways associated with mucosal inflammation, airway hyperresponsiveness and airway remodelling. Exposure to certain triggers may cause a constriction of the bronchial tubes, which causes the typical asthma symptoms such as wheezing, chest tightness, coughing and shortness of breath. The intensity of symptoms varies over time along with variable (later possibly persistent) expiratory airflow limitation. Modern diagnostics includes spirometric testing of variable expiratory airflow limitation, bronchial provocation tests and/or allergy testing. In addition, the assessment of so called "*type-2 biomarkers*" (eosinophil count in blood/sputum, fractioned exhaled nitric oxide, serum IgE-levels) permits to differentiate "*Type-2 asthma"* (T helper cell 2 driven; mostly eosinophilic asthma) from "*Non-type 2 asthma*" (T helper cell 1/17 driven; mostly neutrophilic, mixed granulocytic or paucigranulocytic asthma). The aim of modern asthma therapy is the prevention of symptoms and exacerbations and stabilization of lung function using *"Disease Modifying Anti-Asthmatic Drugs"* such as inhaled corticosteroids with or without long-acting-beta$_2$ agonist or long-acting-muscarinic antagonists; and the addition of a biologic as a more target-selective treatment in cases of severe uncontrolled asthma.

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The **Charité Research Organisation GmbH** has longstanding experience in the conduction of early phase projects for new asthma medicines. We want to share our asthma expertise in this special Whitepaper that comes in two parts.

In PART 1, the MODERN ASTHMA MANAGEMENT will be presented and the progress in asthma diagnostics and therapy discussed based on current applicable Guidelines including the Global Initiative for Asthma 2023. A special focus is laid on recent research to novel biomarkers for the identification of certain asthma endotypes that can be used in the clinics for modern asthma management.

In PART 2, the ASTHMA DRUG PIPELINE 2023 will be presented and new drug candidates discussed. In addition, the efforts made to provide advanced medical devices to improve drug exposure to the lung will be addressed in some detail. More sustainable medical devices to reduce the Green House Gas effect are already available on the market. We will focus on the different device technologies and their propellants, especially in regard to the Carbon Footprint and contribution to the Global Warming Potential.



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## Introduction

Asthma is a major serious global health problem, affecting both children and adults. About 262 million people worldwide were affected by asthma in 2019 leading to 455 000 deaths [Global Burden of Disease Study 2019]. However, one can expect that asthma is highly underdiagnosed in dependence of capacity of the respective health care system. In Germany, the prevalence of asthma is about 8.0 % of the adult population, women (9.1%) are more frequently affected than men (7.0 %) and similar across all age groups, and without differences by education [GEDA 2019/2020-EHS].

Asthma is a chronic inflammatory disease of the airways [GINA 2023]: Asthma involves mucosal inflammation with activated eosinophils, mast cells and lymphocytes and airway remodelling with mucosal metaplasia, thickening of bronchial smooth muscles, fibrosis and angiogenesis [Holgate et al., 2015] (**Figure 1**).

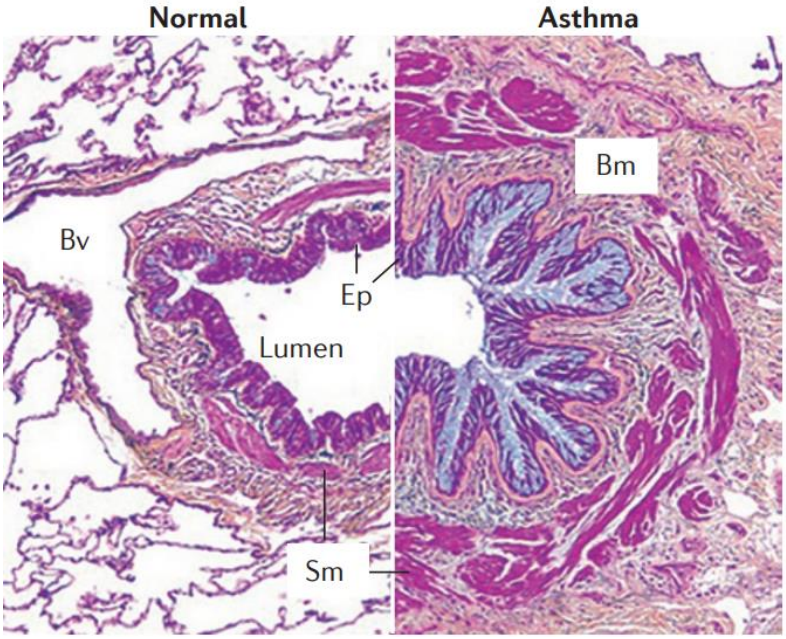


**Figure 1: Cross section of a severe asthmatic airway (right) compared with a normal airway (left).**
Bm, basement membrane; Bv, blood vessel; Ep, epithelium; Sm, smooth muscle
*Source: Figure adopted from Holgate et al., 2015.*

At the same time, the airways become overly sensitive to various stimuli - this is called airway hyperresponsiveness. Exposure to house dust or grass pollen may cause a constriction of the bronchial tubes, which causes the typical asthma symptoms such as wheezing, chest tightness, coughing and shortness of breath. The intensity of symptoms varies over time along with variable (later possibly persistent) expiratory airflow limitation. Modern diagnostics includes spirometric testing of variable expiratory airflow limitation, bronchial provocation tests and/or allergy testing. In addition, the assessment of so called "*type-2 biomarkers*" (eosinophil count in blood/sputum, fractioned exhaled nitric oxide (FeNO), serum IgE-levels) permit an endotyping of asthma.


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The aim of modern asthma therapy is the prevention of symptoms and exacerbations and stabilization of lung function using medicines with *"Disease Modifying Anti-Asthmatic Drugs"* (DMAADs) such as inhaled corticosteroids (ICS) with or without long-acting-beta$_2$ agonist (LABA) or long-acting-muscarinic antagonists (LAMA), together with biologics and/or allergen immunotherapy - if required [Lommatzsch 2022].

Since 2002, the Global Initiative for Asthma (GINA) annually publishes the "Global Strategy for Asthma Management and Prevention" (GINA Strategy Report) containing guidance for primary care practitioners, specialists and related health professionals, based on the latest high quality evidence available. The GINA 2023 report includes a stepwise approach to ongoing treatment for adults, adolescents and children 6-11 years with the clear recommendation to initiate ICS-containing treatment as soon as the diagnosis of asthma is made [GINA 2023]. All patients should also be prescribed a reliever inhaler for quick symptom relief, preferably an *anti-inflammatory reliever* containing both a low-dose ICS and a rapid-acting bronchodilator such as budesonide-formoterol or beclomethasone-formoterol. The intention is to achieve the best possible asthma control and eventually remission of the disease, avoiding exacerbations and educate the patient about the treatment tools managing the disease themselves mainly. The use of a single inhaler with ICS-formoterol with a maintenance dose for every day and the use of the same medication as needed for relief of asthma symptoms ("Single Inhaler Maintenance and Reliever Therapy", SMART) is the preferred option at each GINA treatment step [Lommatzsch 2022, GINA 2023]. The SMART approach is especially advantageous in terms of treatment compliance. Novel biologics targeting inflammatory cytokines allow specific treatment of the different asthma types such as eosinophilic and non-eosinophilic asthma. At current, the use of biologics is limited to the treatment of uncontrolled severe asthma before administration of an oral corticosteroid (OCS). The latter should be given only in case of biologic failure.

The inflammatory bronchi are an open gate for acute bacterial or viral infections that cause exacerbation with bronchospasm, in particular in immunocompromised patients. Evidence does not support the routine use of antibiotics in the treatment of acute asthma exacerbations unless there is strong evidence of lung infection. Timely antibiotic protection is not subject of this article as well as physical trainings to maintain any muscle for sufficient ventilation.


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## Risk Factors and Triggers

Several risk factors have been linked to an increased risk to develop asthma, such as a large genetic predisposition reaching as much as 55% in adults and up to 90% in children [Hernandez-Pacheco et al., 2019]. Asthma is more likely in people who have other allergic conditions, such as atopic dermatitis and rhinitis (hay fever). The exposure to certain environmental factors, such as viral infections or allergens, may at least partly explain why some susceptible children develop asthma whereas others do not [Qui et al., 2019]. Genome-wide association studies (GWAS) have identified thousands of genetic variants associated with asthma development. The majority of the identified genetic variants are not associated with altered protein function but are instead enriched in non-coding gene regulatory elements that can control gene expression and are heavily influenced by epigenetic modifications as identified by epigenetic-wide association studies (EWAS) [Stikker et al., 2023]. As a result, current asthma management includes biologicals targeting proteins that have been extensively associated to asthma in GWAS and EWAS data, including IL-5, IgE, and thymic stromal lymphopoietin (TSLP).

Typical asthma triggers include physical or irritant exposure, change in weather patterns, respiratory infections, tobacco smoking, allergens/mite dust allergy, or exposure to pollutants in certain occupational groups leading to allergic airway sensitization [Lambrecht and Hammad, 2009] (**Figure 2**). Unpredictable asthma triggers such as viral infections, allergen exposure, pollution or stress may cause severe exacerbations. Wherever possible, avoidance of triggers should be part of every patient's written asthma action plan.

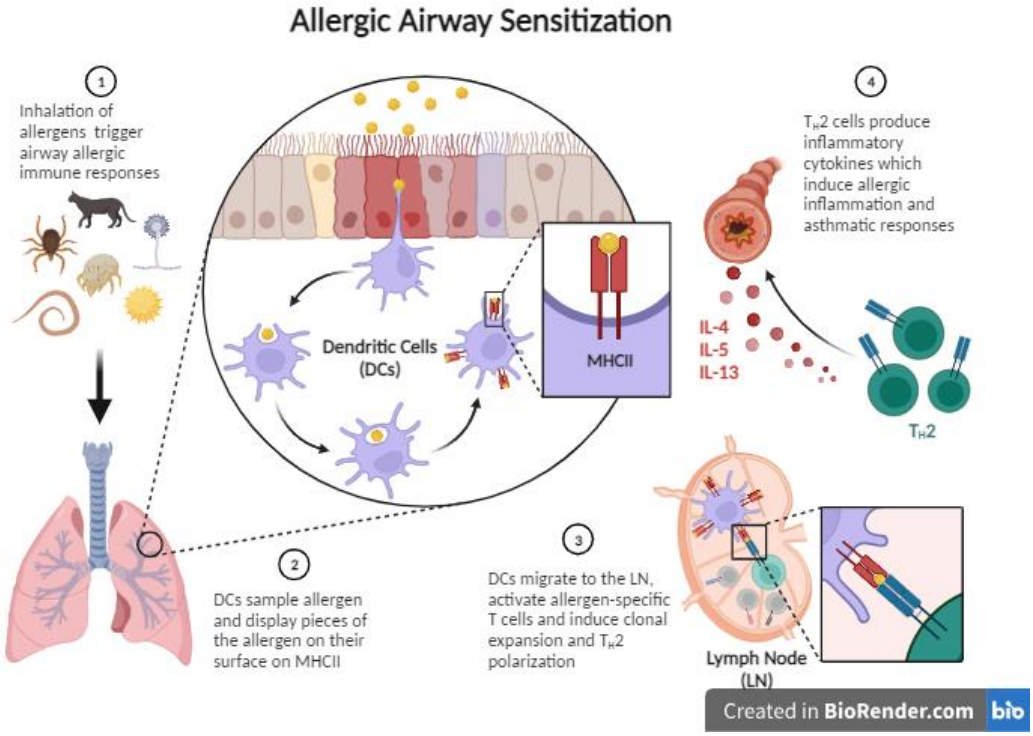


**Figure 2: Asthma triggers**

*Source: Figure adopted from illustrations in Lambrecht and Hammad, 2009*



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## Phenotypes

Asthma is a heterogeneous disease. Each asthma patient can be attributed a certain cluster of clinical traits called asthma phenotype. Among others, the following characteristics are of importance: the temporal pattern of symptom manifestation [Fuchs et al., 2017] (**Figure 3**), the presence or absence of allergy/atopy and related biomarkers, known symptom triggers, disease severity, treatment response to ICS, and risk factors such as obesity.

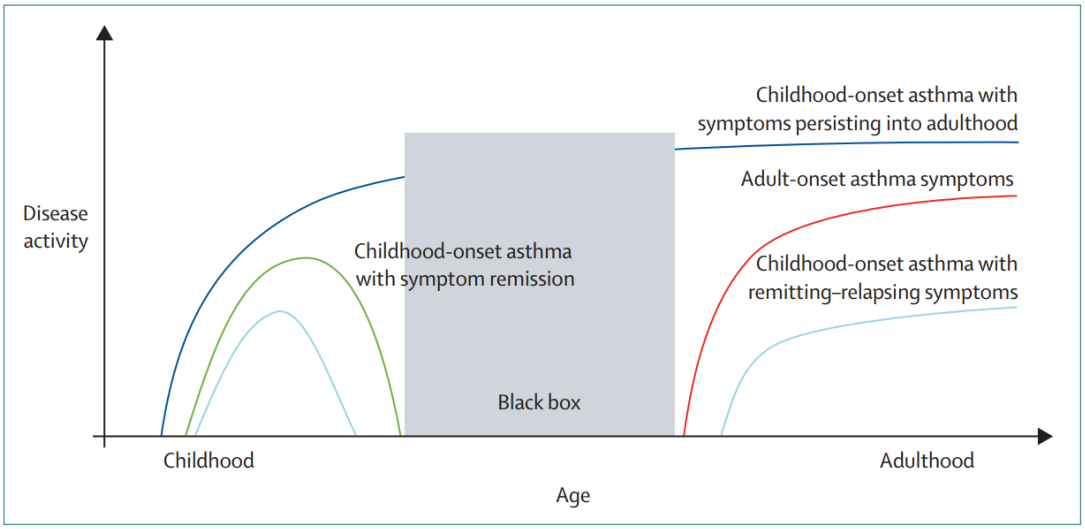


**Figure 3: Temporal patterns of asthma symptom manifestation**
*Source: Fuchs et al., 2017*

According to **GINA 2023**, the following asthma phenotypes are currently distinguished:

*Allergic asthma*: Mostly childhood onset associated with allergic disease/atopy; sputum with eosinophilia *before* ICS use. Allergic asthma usually responses good to ICS treatment.

*Non-allergic asthma*: Absence of allergic history, sputum with neutrophils and few eosinophils or other inflammatory cells; lower and/or delayed response to ICS.

*Adult-onset (late-onset) asthma*: Mostly adult females without allergy history; need higher ICS doses or are ICS-refractory. Those patients often report about occupational triggers.

*Asthma with persistent (or only partially reversible) bronchial obstruction*: few patients with mostly long-standing asthma with severe structural remodelling of bronchial airways.

*Asthma in obesity*: a few patients with obesity and marked respiratory symptoms, mild eosinophilic inflammation of the bronchial tract. Obesity can be seen as an endogenous risk factor for disease manifestation, unfavourable course, increased severity and lack of therapeutic response to corticosteroids.


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## Pathophysiology

The pathophysiology of asthma is a result of interactions between damaged epithelial cells and immune cells. Epithelial cell damage causes liberation of so called alarmins such as TSLP, IL-25, and IL-33, which activate mainly CD4+ T helper cells (Th) driven inflammatory responses and airway remodelling. Both allergic and non-allergic asthma are characterized by activation of allergen-specific T helper 2 (Th2) cells, but also by activation of allergen-unspecific innate lymphoid cells (ILC2 cells), resulting in similar patterns of a so called "type-2" airway inflammation or "type-2 asthma" [Lommatzsch et al., 2023]. Based on the type of the immune cells involved in disease pathogenesis, type-2 asthma can be further distinguished into "type-2 high" and "type-2 low" asthma endotypes: type-2 high asthma is associated with Th2 cell-mediated inflammation, while type-2 low asthma is predominantly characterized by Th1 and/or Th17-cell mediated inflammation [Ji & Li, 2023] (**Figure 4**).

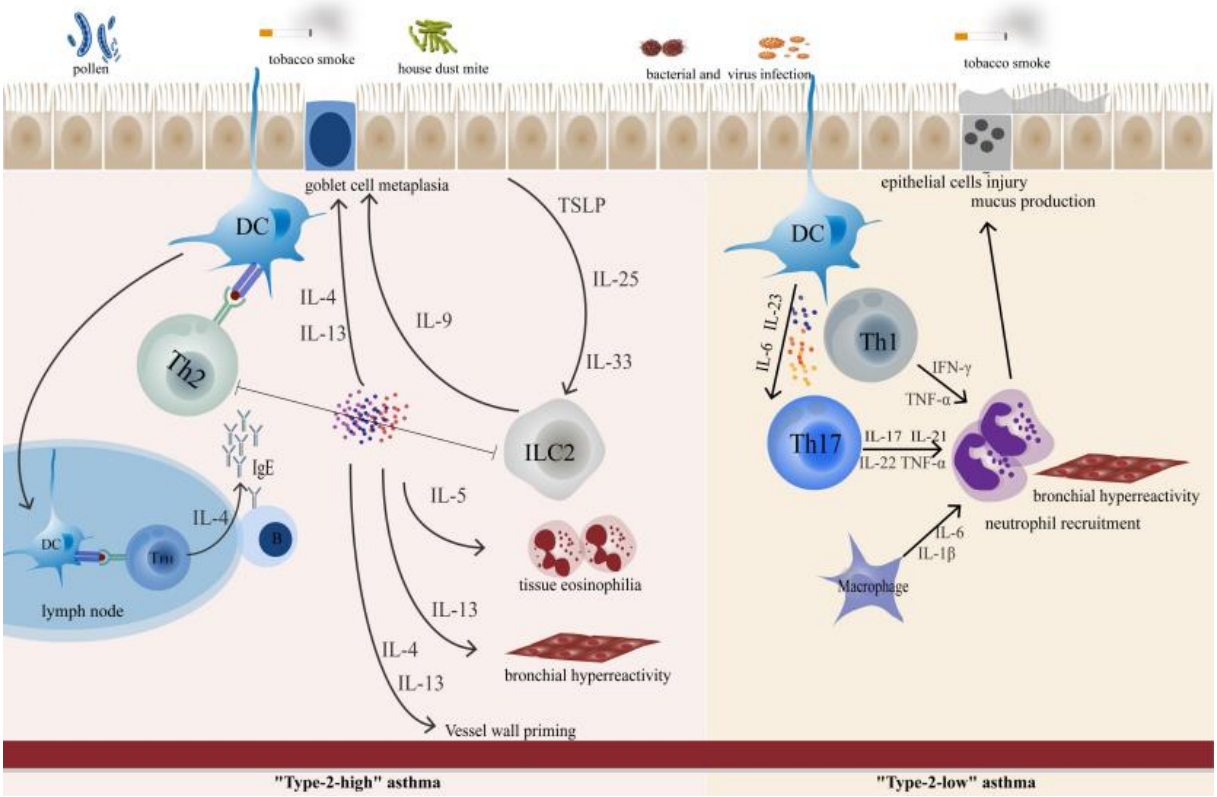


**Figure 4: Type-2 high asthma and Type-2 low asthma**
Left panel: In "type-2 high" asthma, epithelial-derived TLSP, IL-25, and IL-33 can awaken ILC2. Cytokines produced by epithelial cells promote dendritic cell function, polarize CD4+ T cells and promote the polarization of Th2 cells. T follicular helper (TFH) cells control IgE synthesis by secreting IL-4 to allergen-specific B cells. ILC2 derived IL-9 promotes goblet cell metaplasia. IL-5 promotes eosinophil inflammation, while IL-13 and IL-4 are involved in goblet cell metaplasia and bronchial hyperresponsiveness.
Right panel: In "type-2-low" asthma, Th17 and Th1 play an important role in airway neutrophil inflammation and airway remodeling.
*Source: Ji & Li, 2023*


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## Biomarkers

*Biomarkers for Type 2 Asthma*

Biomarkers for type-2 inflammation have been validated in clinical trials using cellular endotyping in blood and induced sputum samples of severe asthma [reviewed in Lommatzsch, 2020], and are meanwhile essential diagnostic tools for the characterization of disease severity, in particular the increased frequency of exacerbations and for the choice of treatment.

The following biomarkers indicate a type-2 inflammation in asthma (GINA 2023):

- Blood Eosinophilic Counts (BEC) ≥ 150/µl, and/or
- Fraction of exhaled Nitric Oxide (FeNO) ≥20 ppb, and/or
- Fraction of Eosinophils in sputum ≥ 2%, and/or
- Asthma is clinically allergen-driven (high serum IgE)

New potential biomarkers are currently *explored* for both asthma endotypes [Theofani et al., 2023] (**Figure 5**):

  - Periostin and IFN-γ serum concentrations in the bronchial lavage (BAL) or sputum *or* neutrophilic accumulation in the airways as indicators for type-2 asthma, and
  - TNF-α (BAL) and YKL-40 (blood) concentrations as indicators for non-type 2 asthma

At current, several potential biomarkers for *TSLP and/or IL-13 target activation* are part of *explorative* pharmacodynamic analyses in clinical trials, among others IL-5 (serum), CCL26 (plasma) as well as thymus and activation-regulated chemokine (TARC) and IgE concentrations (serum).

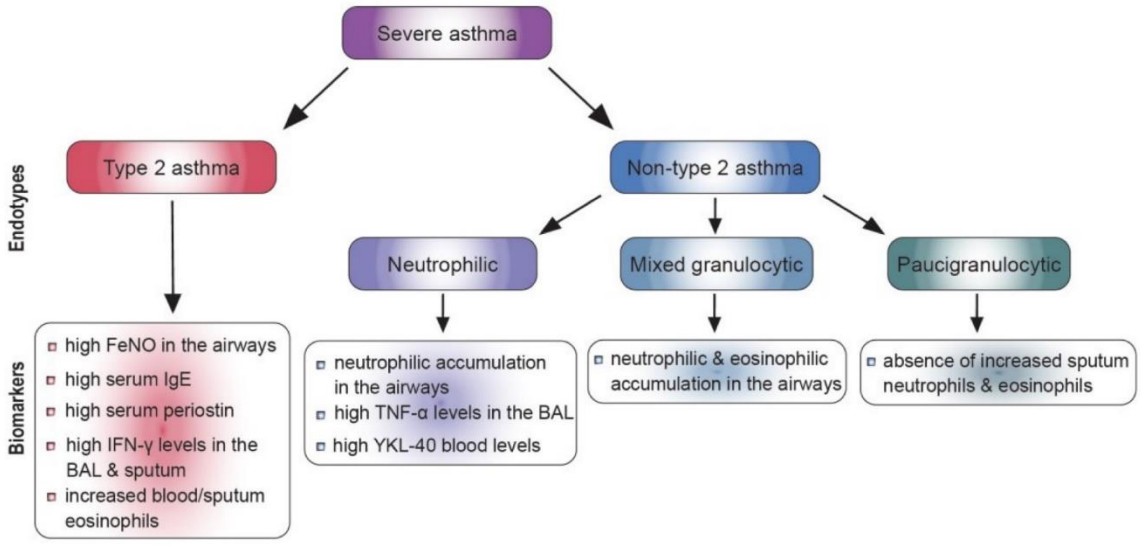


**Figure 5: Endotypes and Biomarkers**
*Source: Theofani et al., 2023*


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The following points should however be considered for the timing of type-2 biomarker assessment [Lommatzsch et al., 2023]: Most patients with mild to moderate type-2 asthma show a good responsiveness to ICS that however might get lost with progression of the disease. Patients with severe asthma are therefore necessitating higher doses of ICS and patients with severe uncontrolled asthma need treatment with a type-2 targeted biologic. At this point, the confirmation of a combination of elevated blood eosinophils and increased FeNO levels is the key to initiate biologics therapy. Both biomarkers are however exposed to *strong individual fluctuations*. The blood eosinophils are often influenced by the time of the last allergen contact and by the season, the FeNO values are strongly influenced by infections or pollutant exposures. Therefore, at least three assessments should be done before excluding type-2 inflammation in severe uncontrolled asthma refractory to ICS treatment. Oral corticosteroids (OCS) are effective in type-2 asthma, but are unfavourable because of their serious side effects and should only be prescribed in case the patient is not responding to the prior biologic therapy or a missing indication. As OCS often suppress type-2 inflammation, the assessment of type-2 biomarkers should be done *before* initiation of OCS or on the lowest possible OCS dose. Otherwise, those counts could be masked as seemingly normal.

### *Omics-based Biomarker Research*

In the 21st century, advanced technologies in transcriptomics, proteomics and metabolomics emerged and facilitated the evaluation of novel "omics-based signatures" in asthma. The enormous growth of genome-wide gene expression datasets for respiratory diseases including asthma allowed systematically screens to identify new asthma relevant genes and molecular pathways for specific asthma phenotypes. Although none of these novel phenotyping strategies translated into clinical practice up to date, they propose potential targets for individual tailored interventions targeting treatable traits (*precision medicine*).

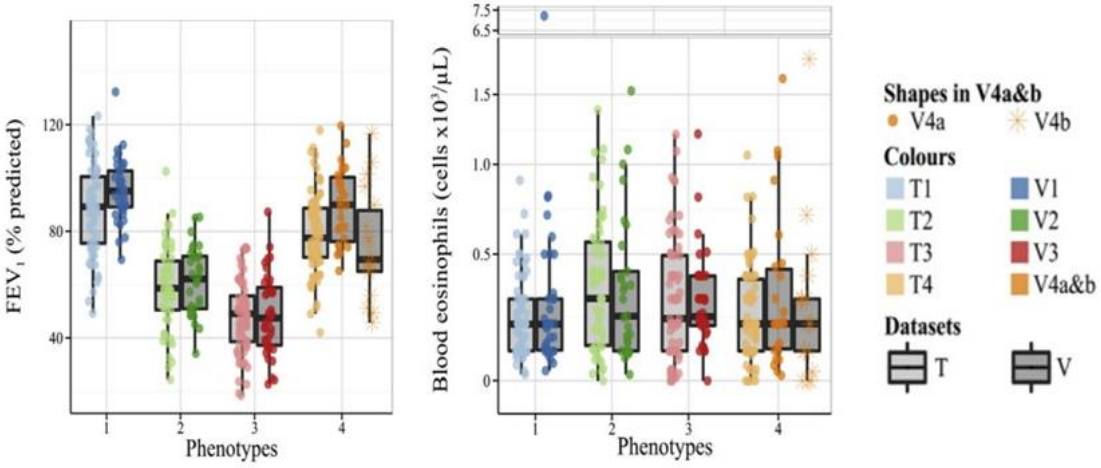


**Figure 6. Box plots of two main variables (% FEV1 and Blood eosinophils)**

Percentage of predicted Forced Expiratory Volume in 1st sec (FEV1) (left panel) and Blood Eosinophil Counts (right panel). Clusters found in the training (T1-T4) and validation (V1-V4a&b) sets exhibit similar distributions (light and dark hue of the same colour). T1/V1 = controlled moderate asthma, T2/V2 = severe late-onset asthma, T3/V3 = severe OCS-dependent asthma, T4/V4a&b = obese females with uncontrolled severe asthma
*Source: Lefaudeux et al., 2017.*


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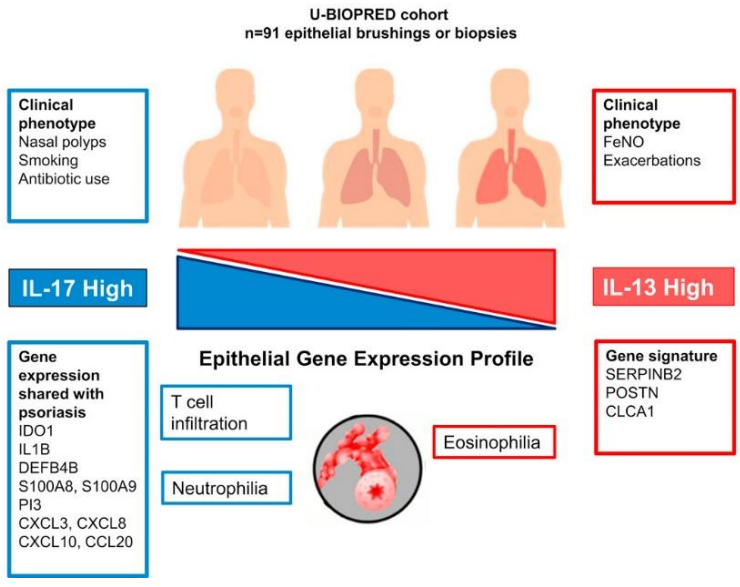
Using whole-genome microarray and quantitative real-time PCR analysis of endobronchial biopsies from mild to moderate asthmatics, Choy et al. (2011) found gene expression patterns of Th2 inflammation and other intercellular communications which correlated significantly with local and systemic measures of allergy and eosinophilia. Among others, these findings were the basis for the development of several tailored interventions including biologics. Large multicentre initiatives, including the U-BIOPRED project (*European Unbiased Biomarkers for the Prediction of Respiratory Diseases Outcomes*), focussed then on the identification of distinct severe asthma phenotypes by linking inflammatory biomarkers derived from "omics" and clinical data. Lefaudeux et al. (2017) performed a proteomics and transcriptomics analysis of sputum samples from the U-BIOPRED adult cohort using eight pre-specified clinical and physiological variables. Three reproducible and stable clusters (phenotypes) with distinct clinical and molecular characteristics were observed in this asthma cohort in the training (T) and validation (V) sets: *severe late-onset asthma* (T2=V2), *severe OCS-dependent asthma* (T3=V3), and *obese females with uncontrolled severe asthma* (T4=V4a&V4b), which all had *higher sputum eosinophilia* than a cluster of *controlled moderate asthma* (T1=V1), with no differences in sputum neutrophil counts and FeNO and serum IgE concentrations (**Figure 6**). The identified three transcriptomic profiles however only partly mirror the yet known asthma phenotypes. The limitation of this (otherwise robust) omics trial is a possible bias for panel selection based on matrix (blood/sputum), technology (qPCR, microarray, RNA sequencing), and the algorithm used for statistics (multiple panel testing).




In another U-BIOPRED study, a quarter of the patients showed an IL-17-high asthma with features of a psoriasis immunophenotype identified by whole genome transcriptomic analyses in samples of epithelial brushings, bronchial biopsies and whole blood [Östling et al., 2019]. Gene signatures induced *in vitro* by IL-17 and IL-13 in bronchial epithelial cells were used to identify patients with "IL-17-High" and "IL-13-High" phenotypes of asthma (**Figure 7**).

**Figure 7: IL-17-high asthma with features of a psoriasis immunophenotype**
*Source: Östling et al., 2019*

The IL-17-high asthma phenotype was characterized by bronchial epithelial dysfunction, upregulated anti-microbial and inflammatory responses and included activation of the *thromboxane B2 pathway*, which could be considered as biomarker for this phenotype in clinical trials targeting IL-17.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The finding by Poole et al. (2014) that gene expression in nasal epithelial cells largely mirrors expression profiles in the lung airways in children, leveraged the use of surrogate samples such as nasal brushings instead of bronchial biopsies. Likewise, induced sputum samples are easily accessible and are now broadly used as surrogate samples in the clinics. Gene expression studies utilizing sets of biological samples identified "*Differentially Expressed Genes*" (DEG) in asthmatics compared to healthy people. There is however little or no overlap among the lists of genes obtained using different tissues/cells suggesting asthma-associated genes are likely to show tissue-specific expression patterns. Therefore, an integrative analysis focused on multi-tissue transcriptomics for asthma has been done by Ghosh and co-workers (2020) including the following steps (**Figure 8**):

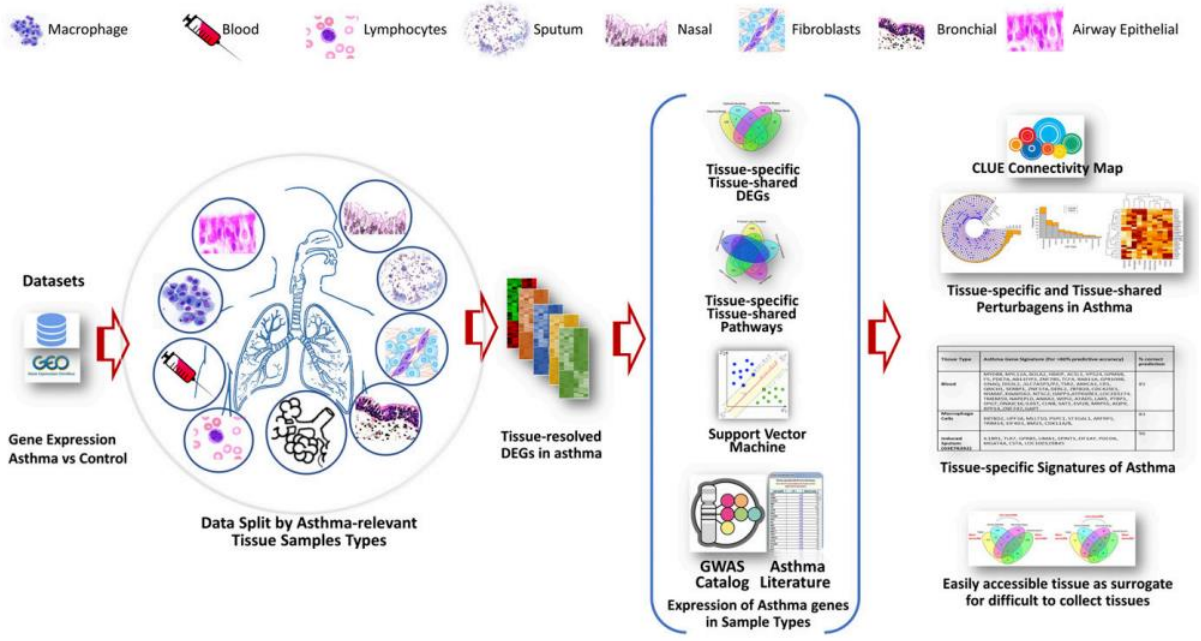


**Figure 8: Diagrammatic summary of the approach starting from the discovery of differentially regulated genes to drug repositioning in asthma using multi-tissue transcriptomic analysis.** Using asthma transcriptome data identified from multiple sample types such as blood, lung, isolated fibroblasts, nasal epithelium, lymphocytes, and airway macrophages molecular signatures of asthma were identified. The signatures were further connected with asthma genes identified by Genome-Wide-Association-Studies (GWAS). The tissue-resolved molecular signatures were further evaluated for their utility in drug repurposing (i.e. identifying perturbagens via connectivity map analysis to reverse asthma signature).
*Source: Ghosh et al., 2020*

A key finding of this study was that DEGs related to asthma *do not* significantly overlap between tissues, but rather overlap/participate in complex pathways and networks crucial for asthma manifestation, such as Th2 response (POSTN), inflammation (NOS2, ALOX15) and mucus production (MUC5AC). From the study results, it can be concluded that airway epithelium can be partially represented by the nasal samples whereas induced sputum may partially represent bronchial samples *at the pathway-level* indicating the significance of easily accessible samples as surrogates. Future studies may focus on collecting transcriptomic data from multiple tissues and correlate them to the individual asthma phenotype including data to corticosteroid responsiveness for identification of new treatable traits (*precision medicine*).


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## Diagnostic Algorithm

The diagnosis of asthma is based on the patient's history, characteristic symptoms and evidence of an (at least partially) reversible bronchial obstruction in the pulmonary function tests, treatment response to ICS, and biomarkers of type-2 inflammation. Asthmatics usually report respiratory symptoms such as wheezing, shortness of breath, chest tightness and coughing, which vary over time and in intensity.

Asthma symptoms may resemble symptoms reported by patients with other respiratory or cardiac diseases. For example, it may be difficult to differentiate asthma from chronic obstructive airway disease (COPD). There are however some clinical features to distinguish asthma from COPD [Lommatzsch, 2022] (**Figure 9**).

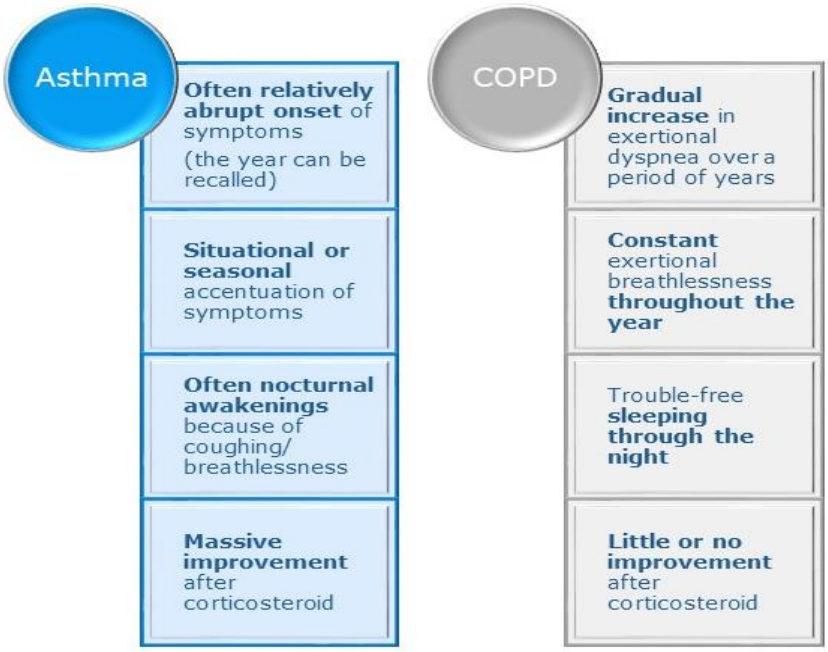


**Figure 9: Anamnestic differentiation between asthma and COPD**
*Source: Adopted from Lommatzsch, 2022.*

Start point of the diagnostic algorithm for asthma is a careful medical history of symptoms (including first onset, situational or seasonal triggers, and course over the last month/year), followed by pulmonary function testing (possible in adults and children > 6 years) and reversibility testing of bronchial obstruction after inhalation of a short-acting $beta_2$ agonist (SABA) such as salbutamol. An increase in the Forced Expiratory Volume in 1st sec (FEV1) of more than 12 % after salbutamol inhalation confirms the diagnosis asthma.

In the absence of reversibility of bronchial obstruction, asthma can also be diagnosed if the patient responds well to corticosteroids, has a typical (type-2) biomarker constellation and/or bronchial hyperresponsiveness or a Peak Expiratory Flow (PEF) variability of more than 20 % (highest of 3 readings using the same meter). In addition, patients who present with asthma symptoms and normal lung function may be diagnosed with asthma in case they have extremely high FeNO concentrations (i.e. ≥ 50 ppb) and are responding to inhaled


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corticosteroids. In contrast, in patients with asthma symptoms, who have a normal lung function, no bronchial hyperreactivity, no typical (type-2) biomarker constellation and do not respond to corticosteroids the diagnosis asthma is unlikely and should be revised [Lommatzsch et al., 2023] (**Figure 10**).

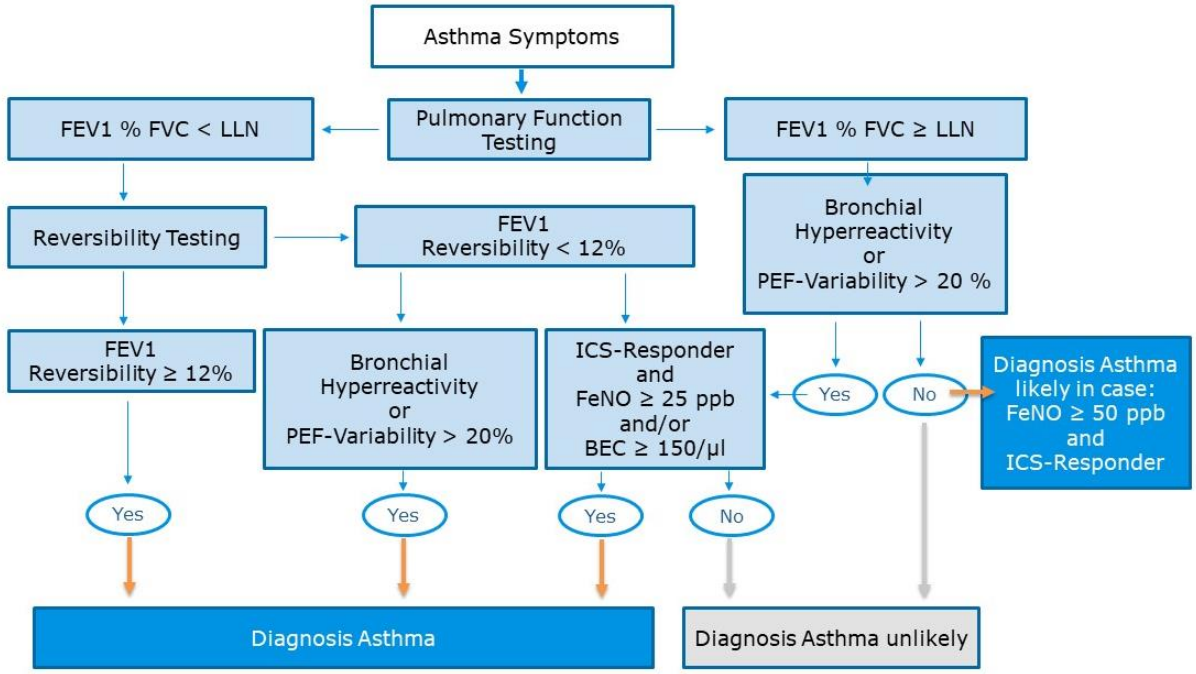


**Figure 10: Clinical algorithm of asthma diagnostics in adults**
BEC: Blood Eosinophils Count, FEV1: Forced Expiratory Volume in 1st sec, FVC: Forced Expiratory Vital capacity, FeNO: Fraction of exhaled Nitric Oxide, LLN: Lower Limit of Normal (corresponds to a z-score of -1.645), PEF: Peak Expiratory Flow, ppb: parts per billion.
*Source: Adopted from Lommatzsch et al., 2023. S2k guideline Specialist diagnosis and treatment of asthma.*

## Allergy diagnostics

Prick tests and specific serum IgE levels for suspected allergen-associated respiratory symptoms may serve to identify patients with the allergic asthma phenotype who often have a history of allergic rhinitis or sensitization to house dust mite. These patients may benefit from either subcutaneous or sublingual allergen immunotherapy. Atopy *per se* does however not satisfy the diagnosis asthma.

## Asthma control (GINA 2023)

A poor symptom control is strongly associated with a higher risk of exacerbations. Therefore, symptom control should be assessed regularly during routine prescribing and treatment dispensing.

The four GINA questions for symptom control are as follows:

| A. Asthma symptom control | | Level of asthma symptom control | | |
|---|---|---|---|---|
| In the past 4 weeks, has the patient had: | | Well controlled | Partly controlled | Uncontrolled |
| • Daytime asthma symptoms more than twice/week? | Yes☐ No☐ | None of these | 1–2 of these | 3–4 of these |
| • Any night waking due to asthma? | Yes☐ No☐ | | | |
| • SABA reliever for symptoms more than twice/week?* | Yes☐ No☐ | | | |
| • Any activity limitation due to asthma? | Yes☐ No☐ | | | |

*Adopted from the Consensus based GINA Symptom Control Tool (GINA 2023, Box 2-2A)*

Potential risk factors for poor asthma outcomes should be assessed at diagnosis and periodically every 3-6 months after starting ICS-containing treatment. Risk factors for exacerbations are for example a low FEV1 (<60% predicted) with high bronchodilator responsiveness or increased type-2 biomarkers (high blood eosinophils and/or elevated FeNO). Lifestyle factors such as tobacco smoking and nutrition habits leading to obesity are known risk factors for poor symptom control and exacerbations. A low compliance with the prescribed ICS (poor adherence or incorrect inhaler technique) and/or an extremely high SABA use (more than 1 canister per month) are predictors of exacerbations even if the patient has few asthma symptoms.

Numerical asthma control tools, such as the Asthma Control Test (ACT) [Thomas et al., 2009] and the Asthma Control Questionnaire (ACQ) [Juniper et al., 1999] can be used in various versions in the clinics including research trials to screen for changes in symptom control.

## Treatment

Already in the ancient world asthma was described as breathing difficulties including shortness of breath; heavy, short breathing, and anxiety and a relationship to environmental triggers was assumed. It was not before the late 19$^{th}$ century, when Sir William Osler specified bronchial spams as the cause of airway inflammation in asthma. The postulation of bronchodilation as the basic principle for relieve of asthma symptoms was followed throughout the 20th century. Medical professionals began to overprescribe bronchodilators with deleterious side effects causing an epidemic of asthma deaths in the 1960s and 1980s. Therefore, more specific bronchodilators such as beta$_2$ receptor agonists that have a short onset of action and can be inhaled were developed to reduce the risk of severe side effects. The short-acting beta$_2$ agonist (SABA) salbutamol and the long-acting beta$_2$-agonist (LABA) formoterol have meanwhile been established in asthma management as so called "*relievers*" which can be used for symptom relief, or before exercise or allergen exposure.

In the 21$^{st}$ century, the enormous progress in genomics and proteomics led to a paradigm change and the acknowledgement of asthma as an immune-triggered disease that requires long-term anti-inflammatory therapy with *"Disease Modifying Anti-Asthmatic Drugs"* (DMAADs) such as inhaled corticosteroids (ICS) with or without LABA or LAMA, together with


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biologics and/or allergen immunotherapy – if required. The administration of ICS with a broad anti-inflammatory action such as budesonide or beclomethasone is targeting symptom control and future risk. Combinations of ICS with formoterol or SABA are *anti-inflammatory relievers* (AIR) which are used as-needed-only. The preferred option at each GINA treatment step is the use of a single inhaler with ICS-formoterol with a maintenance dose for every day and the use of the same medication as needed for relief of asthma symptoms *("Single Inhaler Maintenance and Reliever Therapy", SMART*) is [Lommatzsch 2022, GINA 2023]. The SMART approach is especially advantageous in terms of treatment compliance. In rare cases, the administration of leukotriene receptor antagonists (LTRA) remains an additional option to reduce bronchial hyperreactivity to unpredictable or occupational triggers. The introduction of targeted treatment with biologics for patients with severe uncontrolled asthma has been a fundamental progress. In parallel sophisticated devices for robust use in as well severe asthma attacks have been developed to allow precise dosing with improved pulmonary distribution of the medication-propellant combination.

GINA 2023 and the German S2k-Guideline 2023 both classify asthma by severity and extent of disease. This classification is done in five steps that are used to assess the efficacy of maintenance controller treatment in adults & adolescents and children. In this Whitepaper, we present the GINA 2023 recommendations for adults & adolescents (**Figure 11**).

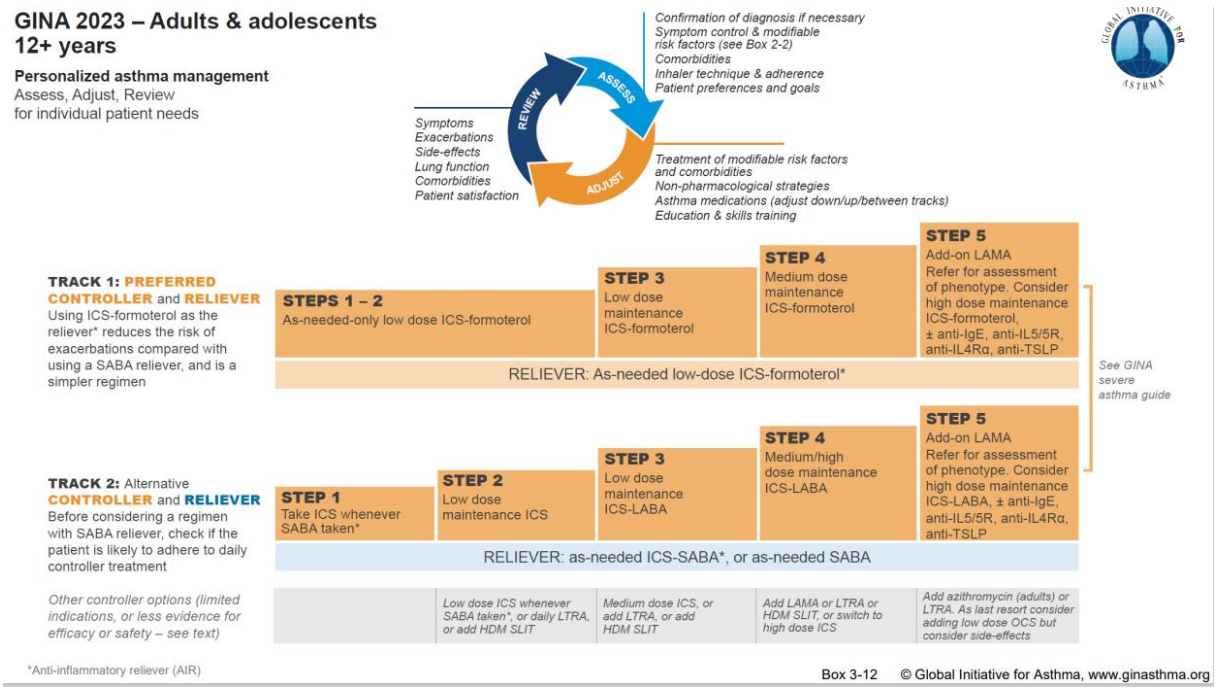


**Figure 11: Personalized asthma management for adults and adolescents (GINA 2023)**
HDM – house dust mite, ICS – inhaled corticosteroid, LABA – long-acting beta$_2$ agonist, LAMA - long-acting muscarinic antagonist, LTRA – leukotriene receptor antagonist, OCS – oral corticosteroids, SABA – short-acting beta$_2$ agonist, SLIT – sublingual immunotherapy.
*Source: GINA 2023*


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Two-track options with either CONTROLLER/PREFERRED RELIEVER (Track 1) or CONTROLLER/ALTERNATIVE RELIEVER (Track 2) are recommended for a personalized asthma management including a continuous cycle of asthma symptom assessment, therapy adjustment and outcome review. The intention is to achieve the best possible asthma control avoiding exacerbations and to educate the patient about the treatment tools managing the disease largely themselves. Patients should be seen 1 to 3 months after treatment initiation and every 3 to 12 months thereafter. After an exacerbation, a review visit within 1 week should be scheduled.

The preferred GINA Step 1-2 treatment for adults & adolescents is low-dose combination ICS-formoterol taken as needed for symptom relief, and if needed before exercise (AIR only). Alternatively, low-dose ICS may be taken whenever SABA is taken. Using ICS-formoterol as the reliever reduces the risk of severe exacerbations compared with using a SABA reliever, and is a simpler regimen. Details to single medications and the required doses on each of the further treatment steps as well as for stepping up or down asthma treatment are listed and commented in GINA 2023, and can be reviewed there. At GINA Step 5, the use of a biologic (before OCS) is now indicated when highest dose ICS-LABA plus LAMA were not sufficient to reduce the exacerbation risk in a patient. Adult patients with persistent symptomatic asthma despite high-dose ICS-LABA may receive also the antibiotic azithromycin on top – if there is evidence of lung infection. To avoid development of antibiotic resistance, azithromycin should only be initiated after specialist consultation.

## Positioning of biologics

Several biologics have meanwhile been approved for the treatment of severe uncontrolled asthma despite others who failed [Ji & Li, 2023]. Depending on their target(s) they can be used for either type-2 *high* or type-2 *low* asthma or both (**Figure 12**). All of the FDA approved biologics are now also approved by EMA and are available on the European market.

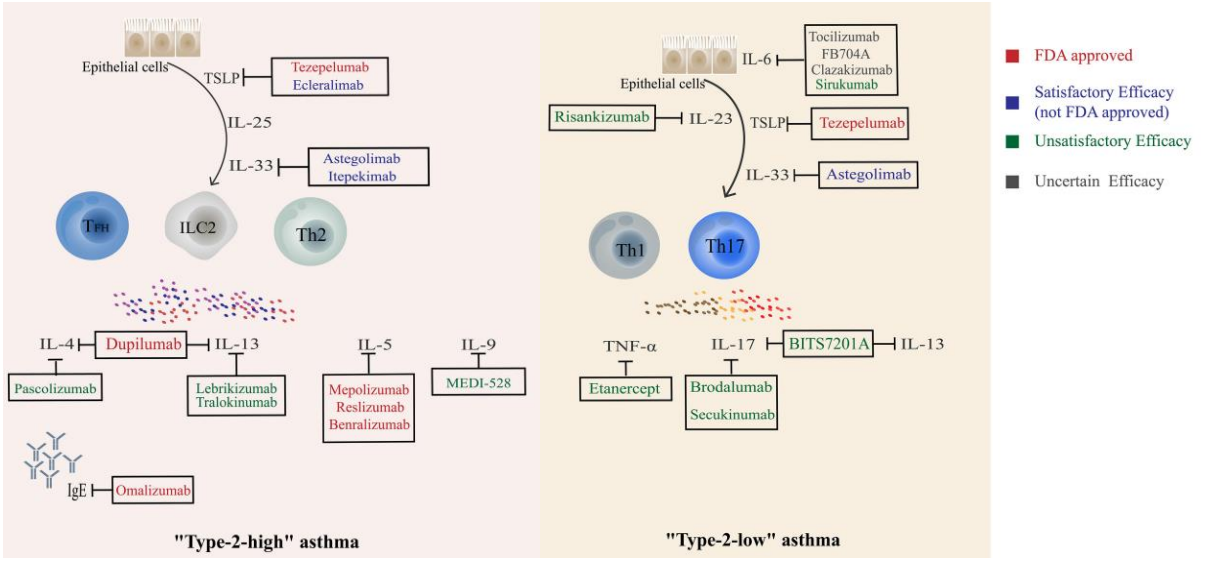


**Figure 12: Current biological agents targeting Th cells and related cytokines.**
*Source: Ji & Li (2023)*


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According to the German S2k-Guideline 2023, the type of biomarker has to be considered when choosing a biologic for a patient with persistent symptoms under medium/high dose ICS-LABA (GINA Step 4 to 5):

- Patients who have *high* type-2 biomarkers (FeNO ≥ 50 ppb and/or blood eosinophile count ≥ 300 cells/µl) should continue ICS-LABA at the highest possible dose for at least 3 months (according to the ICS dosing table) before starting a biologic for type-2 *high* asthma including anti-IL-5-R (mepolizumab, reslizumab or benralizumab), anti-IL4/13-R (dupilumab), anti-TSLP (tezepelumab), or in case of allergic asthma (high serum IgE concentrations) anti-IgE (omalizumab).

- In patients who have *low* type-2 biomarkers (FeNO < 20 ppb and/or blood eosinophile count < 150 cells/µl) a LAMA should first be added such as tiotropium in a mechanical single-nozzle nebuliser (Respimat®) or glycopyrronium as part of ICS/LABA/LAMA fixed combinations (currently approved are mometasone furoate/ indacaterol/glycopyrronium as a powder inhaler and beclomethasone/formoterol/ glycopyrronium as a metered dose inhaler. If there is no response to LAMA, these should be discontinued and a biologic should be started. At current, the only biologic that has been approved for type-2 *low* asthma is tezepelumab. TSLP is also secreted by drivers of type-2 *low* asthma such as neutrophil granulocytes, which may explain tezepelumab efficacy also in type-2 *low* (non-eosinophilic) asthma.

### Treatments no longer recommended

Due to the increased risk of asthma-related death and worse outcome in patients treated with SABA-only (compared with ICS), GINA 2023 no longer recommends SABA-only treatment of asthma in adults, adolescents or children 6-11 years. Likewise, the use of regular or frequent LABA or LAMA without ICS increases the risk of exacerbations and is therefore strongly discouraged. The use of theophylline and chromones is no longer recommended because of their weak efficacy. In addition, theophylline at higher doses may cause life-threatening side effects.

### Uncontrolled asthma/Difficult to treat asthma/Severe uncontrolled asthma

Beside the tremendous progress in asthma therapy, a substantial percentage of asthma patients still suffer from *"uncontrolled asthma"* characterized by poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma) and/or frequent exacerbations (≥2/year) requiring an OCS, or serious exacerbations (≥1/year) requiring hospitalizations. Despite a high intensity treatment, usually consisting of high dose ICS-LABA, a significant part of them are categorized as *"difficult to treat asthma"* mostly due to an incorrect inhaler technique, poor adherence, smoking or comorbidities, or because of a wrong diagnosis [GINA 2023, Chung et al., 2014] Around 4 to 5 % of asthma patients are evaluated as *"severe uncontrolled asthma*", i.e. those patients with "difficult to treat asthma" despite good adherence and inhaler technique [Hekking et al., 2015; Backman et al., 2019].


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### Remissions

Despite spontaneous remissions in the transient asthma phenotype in children, remissions in adults (no symptoms/ exacerbations, no asthma medication for at least 1 year) may occur after a therapeutic intervention (off treatment) or during therapy (on treatment). So far, there is only one longitudinal study reporting that about 16% of adults with recently diagnosed asthma may experience clinical remission within 5 years [Westerhof et al., 2018]. Further research is on demand to identify significant new targets and treatment approaches to increase the number of remissions in asthma patients.

## A²BCD guide for the practical management

Since the implementation of complex asthma guidelines in non-specialised care remains challenging, an easy-to-understand and concise guide for general practice has been proposed by Lommatzsch et al., 2023 (**Figure 13**).

The guide includes a practical logarithm for *Asthma Diagnostics* & *Treatment* Approaches (A1: Assessment of diagnosis and phenotype; A2: Assessment of current control and future risks) (B: Basic measures; C: Identification and treatment of comorbidities; and D: Individually targeted, phenotype-specific treatment with DMAADs).

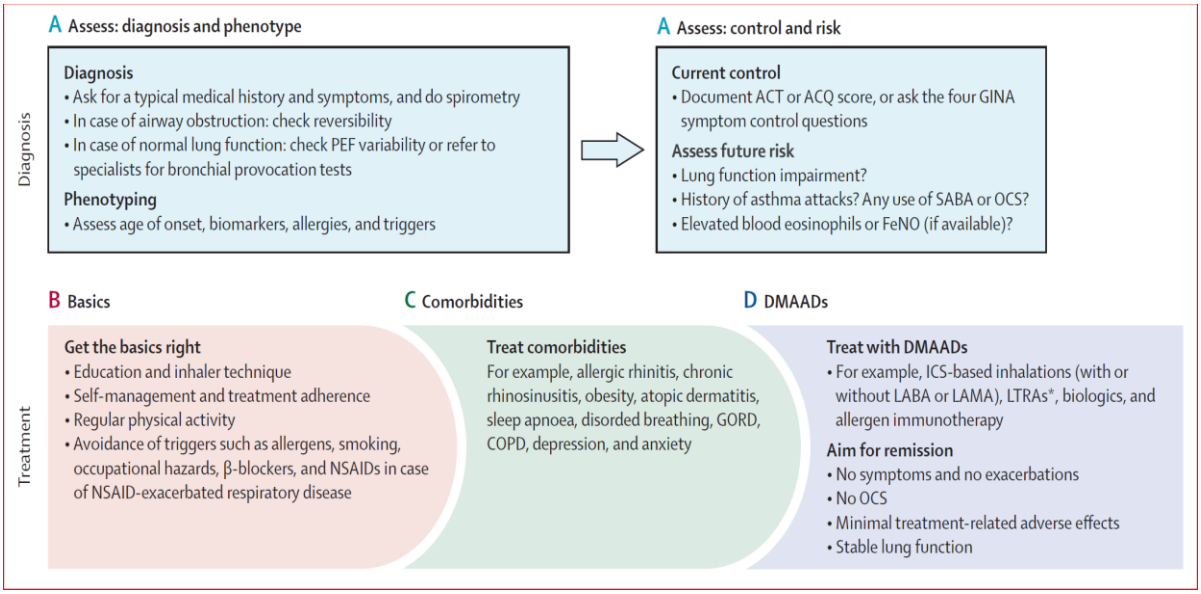


**Figure 13: A²BCD guide for asthma management**

ACQ=Asthma Control Questionnaire. ACT=Asthma Control Test. COPD=chronic obstructive pulmonary disease. DMAAD=disease-modifying anti-asthmatic drug. FeNO=fractional exhaled nitric oxide. GINA=Global Initiative for Asthma. GORD=gastro-oesophageal reflux disease. ICS=inhaled corticosteroid. LABA=long-acting β-adrenoceptor agonist. LAMA=long-acting muscarinic receptor antagonist. LTRA=leukotriene receptor antagonist. NSAID=non-steroidal anti-inflammatory drug. OCS=oral corticosteroid. PEF=peak expiratory flow. SABA=short-acting β-adrenoceptor agonist. *ICS-based therapies are preferred over LTRAs, which are currently used with reservation due to moderate efficacy and possible adverse effects [US FDA black box warning].
*Source: Figure adopted from Lommatzsch et al., 2023*

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