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# Childhood asthma in the new omics era: challenges and perspectives

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**Purpose of review**
Childhood asthma is a heterogeneous inflammatory disease comprising different phenotypes and endotypes and, particularly in its severe forms, has a large impact on the quality-of-life of patients and caregivers. The application of advanced omics technologies provides useful insights into underlying asthma endotypes and may provide potential clinical biomarkers to guide treatment and move towards a precision medicine approach.

**Recent findings**
The current article addresses how novel omics approaches have shaped our current understanding of childhood asthma and highlights recent findings from (pharmaco)genomics, epigenomics, transcriptomics, and metabolomics studies on childhood asthma and their potential clinical implications to guide treatment in severe asthmatics.

**Summary**
Until now, omics studies have largely expanded our view on asthma heterogeneity, helped understand cellular processes underlying asthma, and brought us closer towards identifying (bio)markers that will allow the prediction of treatment responsiveness and disease progression. There is a clinical need for biomarkers that will guide treatment at the individual level, particularly in the field of biologicals. The integration of multiomics data together with clinical data could be the next promising step towards development individual risk prediction models to guide treatment. However, this requires large-scale collaboration in a multidisciplinary setting.

**Keywords**
biologicals, childhood asthma, endotypes, omics, precision medicine

## INTRODUCTION

Childhood asthma is a heterogeneous disease. Asthma classification is typically based on endotypes, which are defined as subtypes of a disease based on shared pathophysiological mechanisms. The introduction of novel treatments with biologics targeting type 2 inflammation pathways urges the development of clinical decision-making tools to guide therapy based on underlying asthma endotypes driving the disease in an individual patient. Access to novel treatment options with biologicals is currently quite random and relies on very few and crude indicators. A personalized medicine approach may benefit the patient as unnecessary treatments are avoided by better matching of patients and therapies. In addition, our current understanding of asthma endotypes is limited and most asthma endotypes involve concomitant inflammatory pathways with dynamic interactions between those pathways that may or may not present in all patients, or in each patient at all time points [1].

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## KEY POINTS

- Childhood asthma is a heterogeneous inflammatory disease comprising different phenotypes and endotypes and, particularly in its severe forms, has a large impact on the quality-of-life of patients and caregivers.
- Severe asthmatic patients may benefit from novel therapies with biologicals, however, the inclusion criteria rely on very few and crude indicators, especially for children.
- Integrated omics approach together with clinical data provide a promising tool for patient-tailored precision medicine in childhood asthmatics.
- The newly established international and multidisciplinary PERMEABLE consortium aims to find novel biomarkers that will allow predicting responses to biologicals in young asthmatic patients.

For these reasons, omics approaches might provide novel insights in asthma endotypes [2▪]. This is especially important for pediatric asthma, since data in this population are scarce. The recently published ERS/ATS Task Force report on the management of severe asthma [3] stresses the importance of performing pediatric trials on novel biologicals in children, as well as studies on biomarkers guiding these treatments.

In this review, we highlight the latest developments in various asthma omics fields (genomics, epigenomics, transcriptomics, metabolomics, and proteomics), and describe how these have contributed to our current understanding of childhood asthma endotypes, taking into account challenges and opportunities of the different approaches (Table 1). Lastly, we will discuss the most recent efforts towards integrating different omics approaches and how this could address clinical needs, such as guiding treatment.

## GENOMICS

One of strongest genetic risk predictors for childhood asthma is the 17q12–21 region [4], but it remains unclear which genes are causing this increased risk [5]. Prime suspects are *ORMDL3* and *GSDMB*, but also *GSDMA* and *PGAP3* have been named as potential candidates. There are several other genes strongly associated with asthma, of which *IL33*, *IL1RL1* (encoding the IL-33 receptor, also known as ST2), and thymic stromal lymphopoetin have emerged as promising targets for novel asthma treatments. In addition, a large recent meta-analysis of genome-wide association studies (including almost 24 000 asthma cases, >118 500 healthy controls) identified nine novel loci (adding up 18 loci in total), the majority involved in the immune response to viruses or bacteria [6], underscoring the importance of host defense processes in asthma risk. Although genomics studies have provided more insights into the genetic architecture of asthma, the contribution of single genetic variants to the asthma risk is low [7]. The integration of environmental exposures in genome-wide interaction studies might provide additional risk information and explain part of the missing asthma heritability [8,9].

Various genetic variants have been reported to influence corticosteroid response; however, the results remain largely inconsistent and effect sizes are small, suggesting that a genomic susceptibility alone is not enough to drive asthma treatment outcomes [10▪▪]. Remarkably, the strongest predictor for childhood asthma onset, the 17q12–21 region, has recently also been associated with an increased risk of asthma exacerbations [11] and worse lung function improvement in children treated with

**Table 1.** Definitions of omics: transcriptomics, epigenomics, proteomics, and genomics

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|---|---|
| Genomics | A broad term that addresses the structure, function, mapping, and editing of genomes. For the purpose of this review, this term defines the study of genomic DNA sequences (i.e., single-nucleotide polymorphism) or gene variants and their association with a disease |
| Epigenomics | A study that addresses the complete set of epigenetic DNA changes, that is, DNA methylation or histone modification in a cell or tissue. The term epigenetics describes alterations in gene activity or function that does not involve any changes in the DNA sequence |
| Transcriptomics | A study of the complete set of RNA transcripts that are transcribed from genomic DNA (transcriptome) under given (specific) conditions in cells or tissues with high-throughput methods, such as RNA-sequencing microarrays |
| Proteomics | A large-scale analysis of the complete set of proteins that are produced by a cell or tissue under certain conditions. This term is also commonly used for describing the methods for protein detection and measurements, that is, protein purification or mass spectrometry |
| Metabolomics | A study of small molecule substrates, intermediates, and products of metabolism, collectively known as metabolites, within cells, tissues, or organisms. These small molecules, their interactions, and products of their interactions within a biological system are known as the metabolome |

inhaled corticosteroids (ICS) [12]. These data suggest, that genetic variation in the 17q12–21 region not only increases asthma risk, but also alters a response to treatment. Closer to clinical implementation, is the pharmacogenomics of long-acting beta-2 agonists (LABAs). A large meta-analysis showed that a genetic variant in the *ADRB2* gene (encoding the beta-2 adrenergic receptor) influences the risk of poor response to LABAs in children [13]; 52% increased risk for exacerbation per risk allele when treated with add on LABAs. This variant (rs1042713, Arg16Gly) is relatively common, and a randomized control trial to guide treatment based on this variant is currently ongoing [14]. Such biomarker-guided trial is key to assess the clinical value of adapting treatment-based individual risk profile and move towards a precision medicine approach.

## EPIGENOMICS AND TRANSCRIPTOMICS

Since the epigenome and transcriptome is modified by environmental factors, epigenomic and transcriptomic profiling might provide added value for individual prediction models of asthma outcomes in addition to genomic profiling [15].

A meta-analysis of EWAS (epigenome-wide association studies) [16▪] showed that reduced DNA methylation of specific CpG sites (in genes involved in the activation of eosinophils and cytotoxic T cells) was associated with an increased risk of childhood asthma. However, in cross-sectional studies, it remains unclear whether these observed differences are driving the disease or are effects of the disease. Novel loci differentially methylated in newborns have been demonstrated as potential biomarkers of risk of asthma by school age. At the same time, cross-sectional associations (asthmatic cases/controls) of methylation patterns in children were shown to reflect both asthma risk as effects of having asthma [17▪▪]. A recent EWAS in nasal swabs collected in children found distinct methylation patterns to be associated with asthma onset and asthma characteristics (elevated IgE/FeNO) in genes that may alter the structure and function of epithelial cells [18]. In addition to asthma onset, methylation patterns in peripheral blood have also been associated with ICS treatment response in asthmatic children [19]. However, ICS use *per se* does not seem to have any significant influence on blood methylation profiles [20].

Transcriptomic studies in asthmatic children are scarce. A recent study demonstrated that low gene expression of type I IFN in nasal samples at baseline predicts short-term exacerbation risk in children and, combined with high type 2 inflammation at baseline, creates a specific 'at-risk' immune state, when a child becomes highly susceptible to exacerbations [21▪]. A microarray analysis of immortalized B cells from ICS treated children who were part of a clinical trial using a gene regulatory network approach, showed that cultured B cells from poor responders to ICS had increased antiapoptotic pathway regulation, compared with good responders [22]. A U-BIOPRED study in adults identified five distinct transcriptomic signatures based on nasal brushes when comparing childhood onset with adult onset asthma, which might indicate different underlying pathways [23] and it would be interesting to assess whether similar signatures can be identified in asthmatic children.

Transcriptomics studies are often performed in heterogeneous samples (constituting of multiple-cell types), complicating the interpretation of the results. Yet, recent findings from collaborative American and European efforts suggest that transcriptomics data from whole blood cells (including key genes such as *IL1RL1, IL5,* and *IL17B*) could be used to develop predictive models of atopic asthma [24]. These results warrant further prospective studies incorporating expression data, in conjunction with clinical and other biomarker data, into asthma prediction models [25▪].

Furthermore, single-cell omics approaches (e.g., single-cell RNA sequencing) are emerging [26]. This approach allows for gene expression profiling at single-cell level. Although these approaches are still very costly, it is expected that they will become more widely used in the coming years.

## METABOLOMICS OF EXHALED BREATH

The analysis of the metabolic content of exhaled breath has received much attention in the past years, since it is a noninvasive method with the potential to provide valuable clinical information on processes in lower airways. Breath contains volatile organic compounds (VOCs) that can be of exogenous (bacteria) or endogenous (cellular) origin. VOC detection can be based on individual compound detection or recognition of patterns of VOC mixtures. Although other techniques exist, most studies in the field of childhood asthma have applied gas chromatography–mass spectrometry (GC–MS) to study individual VOCs or eNOSE technology to study patterns of VOC mixtures. GC–MS is still considered the gold standard since it enables identification of compounds that allows to gain insight in pathophysiological processes and to validate the origin of detected compounds. However, its main limitations are the need for highly trained research personnel and the fact that no real-time (online) findings can be obtained [27▪▪]. Electronic

 

noses, on the other hand, are fast, cheap and easy to use and therefore an appealing point of care technology [27▪▪]. Previous studies have shown that VOC measurements can distinguish inflammatory phenotypes of adult patients with chronic respiratory disease [28], can predict loss-of-asthma control in adults [29▪] and preliminary data show that VOCs can even predict efficacy of mepolizumab treatment in adult asthmatics [30]. However, very limited data are available in asthmatic children [27▪▪]. VOCs analysis using GC–MS is able to successfully predict exacerbations in asthmatic children [31,32]. More research is needed to validate VOC analysis for clinical use in pediatric asthma and assess the diagnostic value of a point-of-care eNose test.

## PROTEOMICS

Systems-wide proteomic tools contribute to a better understanding of a (pato)physiological state of a cell and of a local tissue microenvironment. Proteomic data offer a great addition to transcriptomics and genomics asthma studies, given the complex regulation of gene translation that may be influenced by preexisting asthma pathology, abundance of alternative splicing gene variants, and posttranslational modification (PTM) of synthesized proteins, including histone PTM and phosphoproteomics. Several methods are used for quantitative and qualitative measurements of protein expression and production in biological samples, however, nano HPLC-coupled high resolution MS (nHPLC-HRMS) and immunoassays (flow cytometry, ELISA, Western blotting, and immunohistochemistry) are among the most commonly used. Proteomics is a promising tool for sub-phenotyping asthma patients, identification of biomarkers that allows the estimation of a disease progression and severity, or response to therapy. A recent study in adults identified 10 clusters (or proteotypes) with distinct proteomic signatures within the U-BIOPRED cohort subjects. After overlaying sputum granulocyte counts onto the 10 clusters as metadata, three of these clusters were characterized as highly eosinophilic, three as highly neutrophilic, and two as highly atopic with relatively low levels granulocytes. Remarkably, high levels IL-13 and periostin, but low total serum IgE levels were found in clusters with the highest eosinophilia, whereas the most atopic proteotypes showed high levels of total IgE, but moderate levels of IL-13 and periostin, suggesting different underlying mechanisms for some of type 2 asthma variants. For each of these three phenotypes, candidate protein biomarkers were identified and matched transcriptomic data pointed to differentially activated underlying mechanisms [33].

Only very limited proteomic data are available in asthmatic children. A recent study identified IL-8 and IL-10 in the saliva of asthmatic children as biomarkers of bronchial inflammation and obstruction [34]. Another study showed that children with severe asthma have decreased lipoxin A4 (LXA4) concentrations in sputum in comparison with children with intermittent asthma. LXA4 concentrations negatively correlated with leukotriene B4 concentrations and with exacerbation numbers in children with severe asthma. The same study demonstrated *in vitro* a crosstalk between LXA4 and glucocorticoid receptor at the cytosolic level in peripheral blood granulocytes isolated from children with asthma, which may point towards the mechanism behind the reduction in the ability of ICS to impair control of airway inflammation in children with severe asthma [35]. Moreover, a statistically significant negative correlation between FEV1/FVC and sputum neutrophil gelatinase-associated lipocalin and matrix metalloproteinase-9 in obese asthmatic children was demonstrated [36].

## TOWARDS INTEGRATION OF OMICS DATA

The next step should be the integration of omics data with clinical and environmental data. However, a big challenge is the size of the data together with differences in nomenclature among data types, which will require novel analytical procedures and the collaboration with data scientists. Commonly used approaches are currently limited by the three I's – integration, interpretation, and insights. Post integration, these large datasets aim to yield views of cellular systems at high resolution for transformative insights into processes, events, and diseases through various computational and informatics frameworks [37,38]. Single omic analyses may provide some insight into the basis of lung function in children with asthma, but the underlying biologic pathways are still poorly understood. Kelly *et al.* expanded the single omic findings by integrating the previously correlated gene-metabolite modules collected from 1165 asthmatic children. Weighted gene co-expression network analysis clustered 25 060 gene probes and 8185 metabolite features into eight gene modules and eight metabolite modules, where four and six, respectively, were associated with lung function. While gene modules were enriched for immune, mitotic, and metabolic processes and asthma-associated microRNA targets, the metabolite modules were enriched for lipid and amino acid metabolism [39]. Strategies to integrate risk factors from multiple distinct data sets have been hampered by the issue of missing data and lack of methods to deal with that. Krautenbacher

*et al.* collected and analyzed different types of data (questionnaires, diagnostic, genotype, microarray, RT-qPCR, flow cytometry, and cytokine data) from healthy children, mild-to-moderate allergic asthmatics, and nonallergic asthmatics from 260 German children aged 4–14 years. These data were used for building a novel multilevel prediction approach for childhood asthma phenotyping and outcome, which could deal with a missing data structure. Remarkably, this study identified 4PKN2 (protein kinaseN2), PTK2 (protein tyrosine kinase 2), and ALPP (alkaline phosphatase, placental) as the most important variables for classifying childhood asthma phenotype [40].

## UNMET NEEDS AND FUTURE PERSPECTIVES

Despite the large amount of data the new omics era has provided on type 2 high and type 2 low driven patterns of airway inflammation, the only biomarkers that are currently recommended in the GINA guidelines, as well as a recent ERS/ATS Task Force on the management of severe asthma to guide treatment with biologicals: are total and/or specific serum IgE, blood eosinophils, and FeNO [3,41]. Since these recommendations are mainly based on adult studies, it remains unclear how recommendations can be translated to the younger population, since studies in children are scarce and results from adult studies should only be extrapolated with caution. The clinical expression of severe asthma in children differs from adults, but also normal ranges of biomarkers might be dependent on age, that is blood eosinophilia is observed relatively frequently within the pediatric population [42].

To apply the latest omics technology to guide treatment in asthmatic children (Fig. 1), there is a need for biomarker discovery studies on biologics in children, validation studies, biomarker-guided studies, and implementation studies. So far, most published biomarker studies are in the phase of biomarker discovery for asthma prediction, asthma severity, or corticosteroid response. These studies often report associations. Validation studies should include functional validation of biomarkers using ex-vivo models, development of targeted panels of selected omics markers preferably incorporated in a simple clinical test or treatment algorithm, and clinical validation in independent cohorts. Subsequently, biomarker-guided trials need to be performed to assess whether such a clinical test or algorithm outperforms current clinical practice.

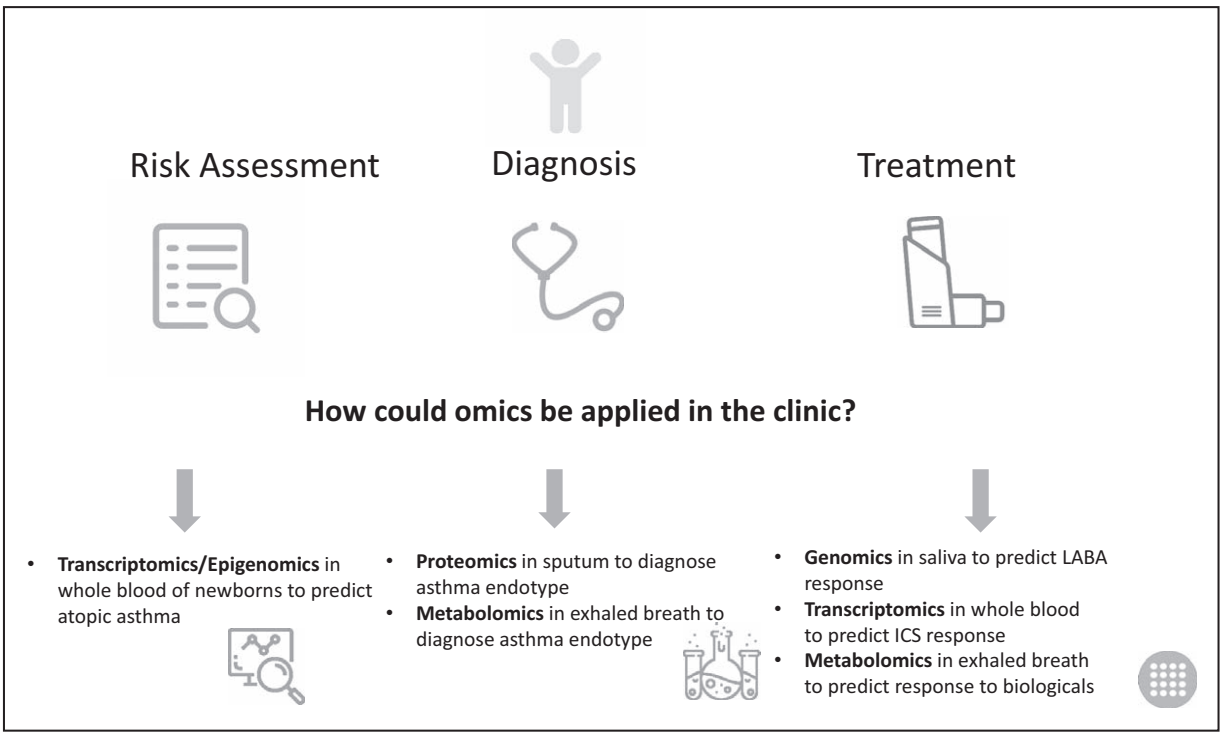


**FIGURE 1.** Application of omics techniques in different aspects of treatment of childhood asthma. Omics techniques may be useful at the stage of assessing the risk of asthma, may help define an endotype, and contribute to the prediction of responses to the given treatment.

Lastly, implementation studies and economic evaluations are needed to assess the clinical utility.

In addition, there is increasing awareness of the role of the airways and gut/airways microbiota in the onset and course of asthma. As microbiome of the gut was shown to participate in the shaping of the immune responses at distal sites, i.e. in the lung, it has become an interesting subject of research with respect to finding associations between microbiota composition and asthma development or severity.

To date, several cross-sectional and longitudinal microbiome studies have been conducted in asthmatics with different phenotypes, which have revealed many associations between bacterial composition and asthma [43]. Similarly, microbial networks of co-occurrence of bacterial genera revealed different bacterial associations across asthma phenotypes [44]. An increasing number of studies reporting on microbiome association with asthma leaves us with a promising tool that in the near future may allow implementing a microbiomic phenotype as a tool for the prediction of disease progression of responses to medications.

To move omics advances towards implementation, we recently established the PERsonalized Medicine Approach for asthma and allergy Biological SeLEction (PERMEABLE) consortium. This multidisciplinary European consortium aims to establish consensus on clinical selection criteria for young biologicals users and combine preclinical studies on treatment response with multiomics biomarker studies of young patients starting with a biological. To incorporate precision medicine to the pediatric asthma clinic, we need to identify and validate predictors of nonresponse to corticosteroids, as well as predictors for response to novel targeted treatments. These predictors should be accurate and preferably as noninvasive as possible. Collaboration and bringing experts from different fields together (such as clinicians, pharmacologists, immunologists, and data scientists) is inevitable to pave the way for more precise, personalized, and effective management of childhood asthma.

## CONCLUSION

Omics studies have largely expanded our view on asthma heterogeneity, helped understand cellular processes underlying asthma, and brought us closer towards identifying (bio)markers that will allow the prediction of treatment responsiveness and disease progression. A next promising step could be the integration of multi omics data together with clinical data, to feed into an individual risk prediction model. However, this requires large-scale collaboration in a multidisciplinary setting.


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### Conflicts of interest

*There are no conflicts of interest.*


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