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Precision medicine in childhood asthma

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Purpose of review
Childhood asthma is a heterogeneous disease and many children have uncontrolled disease. Therefore an individualized approach is needed to improve asthma outcomes in children. Precision medicine using clinical characteristics, biomarkers, and the rapidly involving field of genomics and pharmacogenomics aims to achieve asthma control and reduce future risks with less side-effects in individual children with asthma.

Recent findings
It is not yet possible to select treatment options on clinical characteristics. Novel monoclonal antibodies are efficacious in patients with severe, eosinophilic asthma. Reduced lung function growth and early decline is a prevalent finding in children with persistent asthma. Pharmacogenetic studies have identified children at risk for cortisol suppression when using inhaled corticosteroids.

Summary
Clinical characteristics and simple biomarkers like eosinophils, IgE, and the fraction of exhaled nitric oxide may be used in clinical practice for a basic precision medicine approach, deciding which children will have the best chance to respond to inhaled corticosteroids and to the biologicals omalizumab and mepolizumab.
Further application of pharmacogenomics and breathomics needs additional studies before they can be applied as tools for precision medicine in individual children with asthma.

Keywords
biologicals, biomarkers, childhood asthma, pharmacogenomics, precision medicine

INTRODUCTION

Childhood asthma is a heterogeneous disease with marked variation in age of onset, type of respiratory symptoms, triggers, frequency of exacerbations, lung function, comorbidities, and underlying inflammatory patterns. Therefore an individualized approach may be needed to improve asthma control and reduce future risks such as exacerbations and lung function decline. To unravel the heterogeneity of asthma, research focuses on identifying phenotypes and endotypes that can identify what the biology behind the clinical complaints of a patient is and predict treatment response and the expected course of the disease. In this respect, patient characteristics (e.g., the ones identified in pediatric asthma cluster studies [1]), biomarkers, genomics, and pharmacogenomics may be helpful in targeting asthma treatment and in predicting prognosis.

Most of the children with mild to moderate asthma can reach asthma control with currently available medication. However, their individual response to medication varies. For a small proportion of children with asthma (approximately 2%), current medication is insufficient to prevent exacerbations [2]. In particular, in these children with severe asthma, targeted treatment with biologicals needs a precision medicine approach.

Much attention has been paid to biomarkers related to inflammatory patterns in predicting later risks and targeting asthma treatment. Currently, biomarkers used in clinical practice are eosinophils in blood and sputum and the fraction of exhaled

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KEY POINTS

- Precision medicine in children with asthma aims to select the right asthma medication for the right child, but also to predict future risks like asthma exacerbations, reduced lung growth, and early decline in lung function.
- Pharmacogenomic studies investigating short-acting β-agonists, long-acting β-agonists, and inhaled corticosteroids response heterogeneity resulted in new SNPs to consider for further study as possible targets for asthma treatment.
- Easily available Th2 inflammatory biomarkers like blood eosinophils and the FeNO are the most commonly used biomarkers in clinical practice, in particular in predicting response to biologicals.

nitric oxide (FeNO). Other biomarkers like periostin, markers in exhaled breath, or exhaled breath condensate are used in research settings only.

Pharmacogenomics uses genetic information to predict how patients will respond to their medication both in terms of efficacy and in terms of risk of adverse drug reactions. By extracting genetic information from saliva, pharmacogenomics can be considered as noninvasive and feasible for use in pediatrics.

In this review, we will discuss recent knowledge regarding use of clinical characteristics, biomarkers, and pharmacogenomics in precision medicine in children with asthma, focused on predicting treatment response and future risk.

PREDICTING TREATMENT RESPONSE: CLINICAL CHARACTERISTICS AND BIOMARKERS

Severe asthma

In an analysis of 56 children with severe asthma, improvement in asthma control 2 weeks after treatment with intramuscular triamcinolone was related to phenotypic and molecular predictors [3▪▪]. Clinical predictors considered in this study included race, obesity, prior hospitalization or near-fatal exacerbations, tobacco smoke exposure, sensitization, lung function, FeNO more than 35 ppb, and eosinophilia. No convincing clinical predictors of steroid response were found except for cockroach sensitization. However, several molecular biomarkers, including systemic mRNA expression of inflammatory cytokines and chemokines related to IL-2, IL-10, and tumor necrosis factor signaling pathways strongly differed between children with asthma who did or did not respond to triamcinolone. Another study in 54 children with severe asthma assessed treatment response to systemic steroids in different domains: asthma control, spirometry, and inflammation (sputum eosinophils and FeNO) [4]. Only seven out of 54 children showed response in all four domains, 18 did not respond to any domain. There were no clinical or inflammatory features at baseline such as IgE, blood and sputum eosinophils, and FeNO that were associated with response in any of the outcomes. In contrast, in a study including 107 children with severe asthma, Phipatanakul *et al.* [5▪] showed that baseline bronchodilator response (BDR) and FeNO had good sensitivity and specificity for predicting an increase in prebronchodilator forced expiratory volume (FEV1) after intramuscular triamcinolone. Differences in inclusion criteria, in heterogeneity of the population, and in defining treatment response may explain the different results in these three studies.

Preschool children

Wheezing is very frequent in preschool children and inhaled corticosteroids (ICS) in general only have a modest effect on symptoms. Especially in this age group there is a need for a reliable and easily available predictor of treatment response to ICS or montelukast. In the individualized therapy for asthma in toddlers (INFANT) study, 300 preschool children were included in a double-blind, double dummy crossover study with daily ICS, ICS as needed, and daily montelukast. Children with specific IgE to aeroallergens, blood eosinophil counts at least 300/μl, and particularly the combination of both had the best response to daily ICS compared to ICS as needed and to montelukast [6▪]. Serum eosinophil cationic protein and sensitization to dogs and/or cats also predicted a better response to daily ICS, but the modified asthma predictive index, serum IgE, and Leukotriene E4 in urine did not. In this study no predictors were found to predict a best differential response to ICS as needed or daily montelukast. These data confirm earlier data showing that preschool children with aeroallergen sensitization are more likely to have greater benefits in terms of exacerbations when on ICS compared to placebo [7].

In school-aged children, older studies suggested that a parental history of asthma, increased bronchial hyperresponsiveness, lower lung function, higher BDR, and higher markers of allergic inflammation predicted a better response to ICS as compared to montelukast [8,9].

Fraction of exhaled nitric oxide

A recent study combined easily available clinical features (age at asthma diagnosis >5 years and male

sex) with FeNO 35 ppb or less in a predictive model for steroid nonresponsiveness and found an area under the curve of 0.76 [10]. Earlier studies showed good predictive value of FeNO in response to ICS and differential response to ICS over montelukast in children with asthma [11–13].

Treatment response to biologicals

The introduction of novel anticytokine antibodies, such as anti-IL-5 (mepolizumab and reslizumab) and anti-IL-5 receptor (benralizumab) elegantly showed that it is important to recognize patients who have asthma driven by eosinophilic inflammation. Whereas anti-IL-5 did not improve lung function in patients with unselected persistent asthma [14], this treatment was effective in reducing exacerbations in patients with severe asthma characterized by eosinophilia and recurrent exacerbations [15]. This showed the importance of selecting the right patient and the right outcome.

Blood eosinophils are particularly studied for their predictive value for treatment response to biologicals. Eosinophil counts of more than 300 cells/μl, and also increased FeNO, have been associated with a better response to the anti-IgE antibody omalizumab [16]. For mepolizumab, higher baseline blood eosinophil counts were associated with greater reductions in exacerbations and in improvement of FEV1 and symptoms [17▪]. In patients with eosinophils less than 300/μl, no significant response on exacerbations was retrieved. For reslizumab, significant improvement of FEV1 was shown only in patients with baseline eosinophils of at least 400/μl [18].

A study on dupilumab, an anti-IL4Ra antibody blocking both IL-4 and IL-13, in patients aged 12 years or older with moderate to severe asthma showed a significant reduction of asthma exacerbations, as well as an improvement in lung function and symptom scores. Posthoc analysis suggested that greatest benefit was observed in patients with blood eosinophilia and high FeNO levels [19▪▪]. A second trial in severe asthma patients on oral corticosteroids showed that oral steroid dosages could be reduced in patients on dupilumab, and that these benefits were stronger in patients with blood eosinophilia and high FeNO levels at baseline. However, steroids could also be reduced in patients with no marked blood eosinophilia [20▪▪].

Although the first phase 3 studies of the anti-IL-13 antibody lebrikizumab did not show an effect on major asthma outcomes, in a recent meta-analysis, greater exacerbation rate reductions and FEV1 improvement were shown during treatment with lebrikizumab in adults with high serum periostin levels [21,22▪].

Unfortunately, virtually all studies on biologicals are in adults, with only small numbers of adolescents included. Whether blood eosinophils predict treatment response to biologicals in children with severe asthma remains to be shown.

PREDICTING FUTURE RISK IN CHILDHOOD ASTHMA

Potential outcomes of childhood asthma are reduced lung function growth, persistence of disease with recurrent exacerbations, or alternatively, remission of disease.

Reduced lung function growth

Follow-up of the childhood asthma management program (CAMP) study, a randomized clinical trial (RCT) on ICS, inhaled nedocromil or placebo in children with asthma, classified patients according to four patterns of FEV1 growth, and decline into the third decade of life: normal growth without early decline (25%); reduced growth and early decline (26%); reduced growth only (23%); and normal growth and early decline (26%) [23▪▪]. Risk factors at baseline for abnormal lung function growth included lower FEV1, smaller BDR, more airway hyperresponsiveness (AHR), and male sex. Importantly, already 73 young adults (11%) had lung-function impairments that could be classified as chronic obstructive pulmonary disease. ICS use in childhood was not associated with observed patterns of lung function, questioning whether the outcome of asthma is affected by low-dose ICS. The authors attempted to identify genomic predictors of these patterns in a subsequent study, and found an intergenic single-nucleotide polymorphism (SNP) on chromosome 8 (rs4445257) to be significantly associated with the normal growth with early decline pattern; replication analysis suggested this variant had opposite effects in normal growth with early decline and reduced growth with early decline pattern groups.

In a study from China, 193 asthmatic children were followed for 5 years. One quarter had reduced lung function growth which was associated with lower baseline spirometry, higher FeNO, and female sex. Two SNPs (GSDMB_rs2305480 and IL33_rs1342326) were associated with longitudinal changes in spirometric indices [24▪].

Exacerbations

High short-acting β2-agonists (SABA) use, major psychological problems, exposure to cigarette smoking and allergens in sensitized patients, comorbidities including food allergy and obesity, inadequate

ICS use, low baseline FEV1 and higher BDR, blood or sputum eosinophilia, and high FeNO, are all independent risk factors for exacerbations [25]. A recent study attempted to identify novel biomarkers of risk of exacerbations in cells isolated from peripheral blood mononuclear cells, and showed that the proportion of degranulated basophils was associated with this risk [26▪]. Also, volatile organic compounds in exhaled breath have shown predictive value for exacerbations. In a study in 96 asthmatic children, a combination of seven volatile organic compounds predicted exacerbations in the following 2 weeks with a sensitivity and specificity of respectively 88 and 75% [27]. Although analysis of exhaled breath and exhaled breath condensate has potential as a tool in precision medicine, standardization of collection, preservation, and analysis is a big hurdle [28▪,29,30].

Remission of asthma

Remission of asthma, either defined clinically (absence of asthma symptoms and exacerbations without using asthma medication) or by the strict definition of absence of symptoms, exacerbations, and AHR (complete remission), is a favorable, yet understudied outcome in asthma. In the CAMP study, asthma remission occurred in 229/879 participants (clinical definition) or 111/741 participants (complete remission). Each 10% higher FEV1/forced vital capacity ratio was associated with an increased odds of 4.6 of asthma remission. Other predictors included better AHR and lower blood eosinophil counts [31▪▪]. Good lung function, less severe AHR in combination with absence of blood eosinophilia could predict 80% of remission cases, yet independent replication of this predictive model remains to be shown.

PHARMACOGENOMICS

Over the years, pharmacogenomic studies of SABA, ICS, and leukotriene receptor antagonists have shown inconsistent results [32,33]. In long acting beta agonists (LABA) pharmacogenomics, rs1042713, a coding SNP within the β2 receptor gene, seems to be the most promising SNP to predict asthma control; however, consistent evidence was only found in pediatric studies [34▪].

Lately, only a few studies in pediatric asthma pharmacogenomics have been published.

Short-acting β2-agonists

In a whole-genome sequencing study in 1441 children two new SNPs involved in SABA BDR were identified: rs17834628 and rs35661809, both located on chromosome 5. rs17834628 is located close to *DNAH5*, encoding the making of heavy chain 5, a subunit in outer dynein arms. Dynein is responsible for cell survival functions such as organelle transport. rs35661809 is located close to *LINC01194*, an RNA gene, affiliated with the non-coding RNA class [35▪].

ICS

To investigate ICS response heterogeneity, a genome-wide association study (GWAS) was performed in African American participants (12 years or older) in multiple population groups with asthma [36▪]. The discovery group consisted of 244 patients, who were treated with ICS for 6 weeks. Top associations were validated in three additional groups with African Americans ($n = 803$ and $n = 563$) and Latinos ($n = 1461$). rs3827907 was significantly associated with ICS-mediated changes in asthma control in the discovery ($P = 7.79 \times 10^{-8}$) and validation phase ($P = 0.023$, $P = 0.29$, and $P = 0.041$). This SNP was found to be associated with lower *RNASE2* expression ($P = 6.10 \times 10^{-4}$) in an RNA-seq analysis. Eosinophil derived neurotoxin, the protein product of this gene, is a major constituent of eosinophil cytoplasmic granules and is released systemically upon cell activation [37]. This study provides new information about ICS response variation, as it is the first GWAS in a nonwhite study population to study new SNPs in asthma pharmacogenomics.

Use of ICS is associated with reduced somatic growth and adrenal suppression. The first GWAS on this side-effect was performed in 499 children with two validation cohorts in children ($n = 81$) and in adults ($n = 78$). Adrenal suppression was present in 35 (7%) children in the discovery cohort and six (7%) children and 17 (22%) adults in the validation cohorts. One SNP, in the platelet-derived growth factor D (*PDGFD*) gene locus, increases the risk of adrenal suppression in children and adults who use corticosteroids to treat asthma and chronic obstructive pulmonary disease (COPD), respectively [38▪▪].

LABA

In LABA pharmacogenomics, a candidate-gene study including 400 African American and European American children treated with ICS and LABA was recently published. The study investigated the risk of increased exacerbations in relation to two SNPs within the gene encoding the β2 receptor: the earlier mentioned rs1042713 and rs1042714. Individuals with the homozygous rs1042714 variant were found to be more likely to experience exacerbations versus

those who were heterozygous ($\chi^2 = 6.45$, $P = 0.040$) or homozygous wild type ($\chi^2 = 6.16$, $P = 0.013$). There was no effect shown for rs1042713 [37]. This result was surprising as many studies in pediatrics reported the association between rs1042713 and increased risk of exacerbations [34▪,39–43]. Differences between ethnicities may play a role in the heterogeneity in the results of these SNPs. A Dutch RCT, assessing whether *ADRB2* rs1042713 genotyping leads to better asthma control compared to usual care in 310 children has started in 2018 and will provide answers to the question whether genotyping before step up to treatment step 3 (increase dose of ICS or start LABA) is clinically useful [44].

To conclude, multiple pharmacogenomics studies in childhood asthma have been performed over more than two decades, yet none of the outcomes have been convincing enough to implement in the clinic. Studies investigating SABA, LABA, and ICS response heterogeneity resulted in new SNPs to consider for further study as possible targets for asthma treatment.

DISCUSSION

Asthma is a heterogeneous disease and 'one size does not fit all' given the fact that many children with asthma have uncontrolled disease, experience exacerbations, or are hospitalized for asthma [45]. Precision medicine using clinical characteristics, biomarkers, genomics, and pharmacogenomics may help to select children who will benefit from specific medications and to identify children at risk for exacerbations and reduced lung function growth, while reducing side-effects. It is clear that lung growth patterns are important for the course of the disease, either toward a pattern of airway obstruction fulfilling the spirometric criteria of COPD in early adulthood, as well as predicting asthma remission.

In asthma pharmacogenomics, several new SNPs have been identified during the last years; however, RCTs are largely lacking. Additionally, many genes are involved in response to the different asthma medications and the predictive value for treatment response or risk of adverse events for individual SNPs is relatively low. Although this may hamper the introduction of pharmacogenetics in clinical practice, more and more SNPs are studied for their ability to predict treatment response, combination of genetic data may improve predictive value, genotyping is becoming less expensive, and the first RCTs on precision medicine with pharmacogenomics are on the way [44,46]. In this respect, the identification of an SNP potentially affecting steroid-induced adrenal suppression is promising [38▪▪].

Several widely available biomarkers like eosinophils in blood, IgE, and/or FeNO may be helpful in predicting response to ICS in preschool as well as schoolchildren. Blood eosinophils are particularly helpful in selecting children for targeted but expensive drugs like mepolizumab and omalizumab. Children with severe therapy resistant asthma are underrepresented in trials on biologicals. The 'Severe Paediatric Asthma Collaborative in Europe' tries to bridge this gap by setting up a database on severe asthma in children creating opportunities to collect biomarkers and assess treatment response to biologicals [47].

With the use of portable exhaled breath analyzers like the E-Nose, breathomics may come closer to bedside, especially for diagnosis and monitoring respiratory diseases. Studies on prediction of treatment response by exhaled breath analysis in children are still lacking.

Although clinical characteristics, biomarkers, and (pharmaco)genetic information all have value in predicting treatment response, decision support tools combining all these different domains in a predictive model might eventually help physicians to choose the best treatment for the individual child with asthma. Apart from RCTs, large datasets with real-life baseline data, data on treatment, and on outcomes in several domains may help to develop decision support tools. In future, high-throughput 'omics' technology like genomics, proteomics, and metabolomics can be used to predict treatment response and pave the way toward precision medicine.

CONCLUSION

Clinical characteristics and simple biomarkers like eosinophils, IgE, and FeNO may be used in clinical practice for a basic precision medicine approach, deciding which children will have the best chance to respond to ICS and to the biologicals omalizumab and mepolizumab.

To date, the application of pharmacogenomics and breathomics needs additional studies before they can be applied as tools for precision medicine in individual children with asthma.

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Conflicts of interest

There are no conflicts of interest.

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