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Research Priorities in Pediatric Asthma: Results of a Global Survey of Multiple Stakeholder Groups by the Pediatric Asthma in Real Life (PeARL) Think Tank

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Manchester, London, Aberdeen, Edinburgh, Newport Isle of Wight, and Southampton, United Kingdom; Lille, France; Montreal, QC, Canada; Ankara, Turkey; Valencia and Madrid, Spain; Boston, Mass; Singapore; Brasov, Romania; St. Louis, Mo; Rome, Italy; Santiago, Chile; Brussels, Belgium; Hershey, Pa; Lund and Stockholm, Sweden; Prague, Czech Republic; Groningen, the Netherlands; Warszawa, Poland; Crete and Athens, Greece; Madison, Wis; Cairo, Egypt; Turku and Helsinki, Finland; Perth, Australia; Berlin, Germany; Lisbon, Portugal; Porto Alegre, Brazil; Vienna, Va; Vienna, Austria; Sha Tin, Hong Kong; and Cape Town, South Africa

What is already known about this topic? Our understanding and clinical approach to pediatric asthma remains suboptimal, despite it representing a major health and socioeconomic burden globally. There is a need of high-quality studies in pediatric asthma, to improve clinical outcomes.

What does this article add to our knowledge? In an extensive 2-stage survey of multiple, international stakeholders, we identified and prioritized unmet clinical needs for pediatric asthma. Precision medicine, age-specific recommendations, and prevention were uniformly agreed, unmet needs in pediatric asthma.

How does this study impact current management guidelines? The identified priorities highlight domains that need to be urgently addressed in guidelines. Differential positioning by diverse stakeholders clearly demonstrates the benefit of wide inclusion, but also restructuring of guidelines to reflect the various needs.

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BACKGROUND: Pediatric asthma remains a public health challenge with enormous impact worldwide.
OBJECTIVE: The aim of this study was to identify and prioritize unmet clinical needs in pediatric asthma, which could be used to guide future research and policy activities.
METHODS: We first identified unmet needs through an open-question survey administered to international experts in pediatric asthma who were members of the Pediatric Asthma in Real Life (PeARL) Think Tank. Prioritization of topics was then achieved through a second, extensive survey with global reach, of multiple stakeholders (leading experts, researchers, clinicians, patients, policy makers, and the pharmaceutical industry). Differences across responder groups were compared.
RESULTS: A total of 57 unmet clinical need topics identified by international experts were prioritized by 412 participants from 5 continents and 60 countries. Prevention of disease progression and prediction of future risk, including persistence into adulthood, emerged as the most urgent research questions. Stratified care, based on biomarkers, clinical phenotypes, the children’s age, and demographics were also highly rated. The identification of minimum diagnostic criteria in different age groups, cultural perceptions of asthma, and best treatment by age group were priorities for responders from low-middle-income countries. There was good agreement across different stakeholder groups in all domains with some notable exceptions.
CONCLUSIONS: Different stakeholders agree in the majority of research and strategic (eg, prevention, personalized approach) priorities for pediatric asthma. Stakeholder diversity is crucial for highlighting divergent issues that future guidelines should consider. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1953-60)

Asthma affects over 10% of children in Europe and North America,1 and is expected to exceed 400 million people by the year 2025.2,3 In low- and middle-income settings (LMICs), asthma is the commonest noncommunicable disease in children, with a rising prevalence and more severe disease than that occurring in high-income countries.4 It poses a major health and socioeconomic burden globally, even though the associated mortality has significantly decreased over recent decades.2,5 Although undoubtedly asthma in children and adults has major differences, with diverging mechanisms and triggers, different diagnostics challenges, outcomes, and response to treatments, pediatric asthma is very often approached as an extension of adult asthma. Characteristically, concepts and recommendations are predominantly based on data extrapolated from clinical research studies conducted in adults.2,6 This is engendered by a lack of high-quality interventional, but also epidemiological, pathophysiological, and immunological studies evaluating asthma in childhood. Shortage of data results from ethical and regulatory constraints in conducting research in children and from the relatively lenient criteria for the extension of adult asthma drug licenses to children.7,8

Pediatric Asthma in Real Life (PeARL), a think tank led by international clinical researchers in Pediatric Asthma initiated by the Respiratory Effectiveness Group, was developed to address this deficit. It is an expanding group of experts in pediatric asthma, currently comprising over 40 members from 5 continents and 25 countries, who have extensive relevant track record in research and/or clinical practice of pediatric asthma. The participation of early career researchers and other stakeholders has also been encouraged. PeARL has an open member policy, and health care professionals or researchers with proven expertise (either academic or clinical) in pediatric asthma are welcome to join. Its vision is to develop consensus and recommendations that will improve patient care and limit the disease burden, by capturing and evaluating currently available, clinically relevant evidence, as well as crowdsourcing international expertise on
pediatric asthma. In the long term, we also aspire to conduct and stimulate international, collaborative, high-quality clinical research aiming to address the most salient of the evidence gaps relevant to childhood asthma globally.

We report herein the results of an international multi-stakeholder survey aiming to elicit real-life clinical challenges in pediatric asthma, including asthma in children of preschool age, to identify evidence gaps and unmet clinical needs, and prioritize research and strategic directions, while evaluating the concordance between different stakeholders.

METHODS

This initiative was inaugurated during a face-to-face meeting of international expert clinicians and scientists, aiming to discuss clinical challenges and unmet clinical needs in pediatric asthma (London, United Kingdom, October 2017). We formed a globally representative core group of leading experts in pediatric asthma and related areas (the PeARL think tank), who contributed to the design and conduct of this international survey, which was informed by guidance from the Cochrane Priority Setting Methods Group and published guidance on survey research.

First, we administered an open-question online survey to 28 members of the core group, which comprised international experts in pediatric asthma with clinical and research expertise (over 75% of these members are clinicians evaluating children with asthma in their daily practice, between 100 and over 2000 children per year, in primary, secondary and tertiary care settings; members of this group also have extensive expertise in clinical and/or translational research, evidence-based medicine, and the development of clinical guidelines; they have a mean impact factor of 42.7 and a mean i10 of >100). They were asked to list important unanswered, clinically relevant questions in each of the following categories: (1) definition, (2) natural history, (3) classification, (4) diagnosis, (5) assessment, (6) drug therapy, (7) nondrug management, (8) management of

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TABLE I. Number of unaddressed clinical questions (topics) that were included in each domain and the number of responses that participants were allowed to select

<table>
<thead>
<tr>
<th>Domain</th>
<th>No. of items</th>
<th>Permitted responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, classification, and natural history</td>
<td>13</td>
<td>2-5</td>
</tr>
<tr>
<td>Assessment and monitoring</td>
<td>13</td>
<td>2-6</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>15</td>
<td>2-6</td>
</tr>
<tr>
<td>Non pharmacological management and other questions</td>
<td>16</td>
<td>2-6</td>
</tr>
</tbody>
</table>

exacerbations, and (9) other. We reviewed all responses, resolved duplication, and regrouped and rewrote all identified unique questions in scientific English language. We also produced a plain English version, to ensure that they would be easily understood by patients and the pharmaceutical industry stakeholder groups. The core group reviewed the revised questions and established face validity by confirming that the questions effectively captured the topic under investigation and there were no confusing or (mis)leading questions.

To prioritize these questions, we launched an extensive, second online survey involving different stakeholders: (1) leading experts, defined for the purpose of this survey, as clinical researchers in pediatric asthma, with an overall h-index of at least 30, who have published more than 20 manuscripts on pediatric asthma with at least 15 citations each, in Scopus, during the last decade; (2) researchers, (3) clinicians treating pediatric asthma; (4) patients and their caregivers; and (5) representatives of policy makers, regulators, and the pharmaceutical industry. Group (1) was identified through systematic searches of Scopus; the other stakeholder categories were self-reported by the respondents of the survey (detailed description of the dissemination strategy is available in this article’s Online Repository at www.jaci-inpractice.org).

Respondents had the option to select either a scientific or plain English version of this survey. Both versions are available in this article’s Online Repository at www.jaci-inpractice.org.

In this second online survey, participants were invited by e-mail to undertake a prioritization exercise (SurveyMonkey) in which they were asked to select the most salient unmet needs that could have direct clinical impact on pediatric asthma. Participants were also allowed to select a prespecified number of options (Table I). They also had the option to suggest additional questions. All additional questions were reviewed, recurring questions were presented in the main manuscript, and the remaining questions in this article’s Online Repository at www.jaci-inpractice.org. We compared responses between different stakeholder groups and between participants residing in different continents or countries with different affluence, as classified by the World Bank. χ² and multinomial regression analyses were used to identify between-group differences.

Participants of both stages of the survey were required to provide a valid e-mail, which was used for removing duplication.

RESULTS

Fifty-seven unique, important unanswered clinical questions in pediatric asthma were identified by 26 international experts from 16 countries in 5 continents and prioritized by 412 participants from 60 countries in 5 continents (all but Antarctica, details in Figure 1, and Figures E1, E2 and this article’s Online Repository text at www.jaci-inpractice.org).

Overall, similar responses were observed in the majority of cases across the different stakeholder groups, continents, and economies, suggesting a convergence in relation to unmet needs (Figures 2 and 3, and Figures E3, E4 and this article’s Online Repository text at www.jaci-inpractice.org). Nevertheless, some significant differences were also noted. Both similarities and differences are described in detail below. Responses stratified according to the continent or economy of the country of the respondent are available in this article’s Online Repository at www.jaci-inpractice.org.

Diagnosis, classification, and natural history

The top priorities related to the diagnosis, classification, and natural history of pediatric asthma were: (1) the identification of early risk factors for the development of severe asthma (169 of 412 respondents, 41%); (2) the evaluation of the impact of available interventions on long-term disease progression (162 of 412, 39% of all respondents); and (3) the development of clinical indices or tools able to predict asthma persistence into adulthood (160 of 412, 39%, Figure 2). Responses were similarly distributed across different stakeholder groups, economies, and continents. Notably, patients considered an important priority the prediction of fixed-airway obstruction later in life. Respondents from LMICs, mostly from Africa and Asia, prioritized the identification of minimum diagnostic criteria in different age groups. Participants from LMICs were also interested in the identification of the optimal diagnostic pathway for each phenotype, whereas on the contrary, there was a relative lack of interest from the pharmaceutical industry and organizations on this.

Assessment and monitoring

The identification and validation of diagnostic, prognostic, and therapeutic biomarkers emerged as the most important priority across all categories, as it was selected by 310 of the 412 participants (75%, Figure 3). Although patients and/or caregivers also prioritized this topic, this was to a significantly lower extent compared with other groups. Standardization of the methods used to monitor pediatric asthma and the intervals of follow-up were prioritized by 244 of 412 participants (59%). Moreover, 218 of 412 respondents (53%) considered clarification of the role of systematic and airway inflammation monitoring a priority. Other prioritized topics were age-specific criteria to assess asthma control (168 of 412, 41%) and severity (164 of 412, 39%).

Importantly, patients and their caregivers considered the role of patient-reported outcomes of school monitoring as the highest priorities in this domain. In addition, there was a discrepancy in the prioritization of standardized monitoring of safety, which was prioritized by a significant proportion of clinicians, patients, and caregivers, but less by researchers, experts, and pharmaceutical industry. Safety monitoring was more frequently prioritized by residents of less affluent countries.

Drug therapy

Introduction of precision medicine through clinically relevant endotypes, phenotypes, and/or biomarkers (200 of 412, 49% of the participants) and prevention of airway remodeling (188 of 412 respondents, 46%) emerged as important unaddressed needs (Figure 4). Responses from stakeholder groups were more
heterogeneous in this domain. Patients, caregivers, and clinicians considered criteria for stepping-down treatments an important priority, but that was less reflected in the other groups. Similarly, patients and caregivers considered a priority the development of methods to identify the correct inhaler device for every child and the standardization of asthma management plans, topics that were not prioritized by any other group of stakeholders. Participants from LMICs prioritized the need for direct evidence of efficacy and safety of asthma therapies per age group.

Nonpharmacological interventions and other questions

The interest in nonpharmacological interventions was varied. The evaluation of the role of food supplements, probiotics, prebiotics, and vitamins in the management of pediatric asthma (190 of 412, 46%) was prominent (Figure 5).

Other prioritized questions included: (1) the evaluation of potential differences across ethnicities (180 of 412 participants, 44%), although patients and/or caregivers lacked equal interest in this topic; (2) the criteria for referral for diagnostic assessment by a specialist (174 of 412, 42%), which were only prioritized by respondents residing in more affluent countries; (3) the development of criteria for referral for allergy testing (159 of 412, 38%); and (4) the evaluation of the prevalence and burden of pediatric asthma (157 of 412, 38%).

Finally, people from LMICs prioritized the evaluation of the cultural meaning of asthma in different communities. The increased number of identified priorities in this domain probably reflects the fact that participants were allowed to select a higher proportion of the topics compared with the other domains (up to 3 of 5 responses could be selected).

Additional recurring questions

Participants were encouraged to suggest additional questions that were not included in the preselected list. Recurring suggestions are presented below, whereas the remaining suggested topics are listed in this article’s Online Repository at www.jacic-inpractice.org. Seven participants highlighted the need for methods to improve the adherence of children to asthma pharmacotherapy. Three participants suggested the need for more effective management of acute exacerbations. Three participants highlighted the need to explore interventions that could improve the quality of indoor and outdoor air. Two respondents highlighted the need to incorporate the values and preferences of children with asthma and their families in the development of therapeutic strategies.

DISCUSSION

In an extensive 2-stage survey that reached a wide range of relevant stakeholders, continents, and countries of different income, we identified and prioritized unmet clinical needs for pediatric asthma. Our findings reveal a general agreement among stakeholders for most statements, which provides an optimistic message and increases the validity of the prioritized concepts. A clear need for stratified care, based on biomarkers and clinical phenotypes, but also by age group and demographics has been confirmed. Disease progression and future risk, including persistence of severity, disease persistence into adulthood, and the development of fixed airway obstruction, emerged as the highest concerns. Notwithstanding the need for intensification of research efforts in this domain, a key difference between adult, pediatric patients, and caregivers becomes apparent: the hope and expectation of modifying the natural history of the disease and preventing long-term sequelae, more than addressing current symptoms and control.

Despite the general agreement in priorities, there were some notable differences across the stakeholder groups. Although clinicians’ views were closer to those of patients and their caregivers, not all patients’ priorities were matched by experts and the pharmaceutical industry interest. This highlights the importance of involving the whole range of stakeholders in research, guidelines, practice parameters, and policy design. Caregivers of children with asthma focused more on the safe and correct use of available medications and devices. Characteristically, they prioritized the development of criteria for stepping-down treatments, methods to monitor the disease at school, to identify the correct inhaler device for every child, and to optimize the implementation of written or electronic asthma management plans. They also highlighted the need to further explore the role of patient-reported outcomes. These topics, which were a lower priority for the other groups, clearly reflect everyday challenges for children with asthma and their caregivers. There is a paucity of data looking into the safety and indications of treatment step-down in children, and although a poor inhaler technique is a prevalent cause of uncontrolled asthma, there is still limited evidence on how to successfully improve it. This should serve as a reminder that apart from the relatively small group of children with severe, difficult-to-control asthma who require novel and advanced therapeutic approaches, there is an abundance of children with milder asthma that would benefit from simpler
interventions, for which data are still insufficient. This may also reflect their need for more information and guidance by physicians toward caregivers. This could be challenging in the limited time that a pediatrician or general practitioner can devote to a patient during a visit, and may require different approaches, such as patient groups or community-based education.

Some key differences in priorities for those in LMICs compared with those in high-income areas emerged. Diagnostic challenges and developing diagnostic criteria for children of different ages, cultural meaning of asthma in different communities, and the need to stratify treatment options by age were priorities identified mainly by respondents in LMICs. Given the large childhood population in LMICs and the high prevalence of severe disease in these areas, these should be considered as pressing priorities by both researchers and guideline makers.

Seven years ago, the European Academy of Allergy and Clinical Immunology in collaboration with the European Federation of Allergy and Airways Diseases Patients’ Associations published a position paper summarizing research priorities in allergy, which were identified through consensus among officers of the organizations. In the same year, the International Primary Care Respiratory Group published research priorities identified through an international Delphi survey of primary care physicians. Priorities for pediatric asthma included the conduct of age-specific studies, the development of noninvasive diagnostic tools, interventions toward asthma exacerbations, and evaluation of long-term effects of immunotherapy in children. Our survey reveals that most of these issues still remain unaddressed.

Several methodologies have been suggested for the prioritization of research topics. Delphi surveys aiming to reach consensus among the participants are used extensively. However, group pressure is a known limitation, which may mask differences across the different stakeholder groups. Specifically, differences in the perceived importance of research questions by non-specialists, patients, and their caregivers, who may be more susceptible to group pressure, may be missed.
frequently used approach suggested by the Child Health and Nutrition Research Initiative suggests that all identified research questions should be scored against 5 criteria: (1) answerability, (2) effectiveness, (3) deliverability, (4) potential for substantial reduction of disease burden, and (5) the impact on equity.24 This method aims to prioritize the research questions that are perceived to have the best value for money. Both methodologies aim to select a limited number of research priorities, selected either on the basis of consensus or predicted value for money. Although this may be useful for regulators or funding agencies seeking to prioritize projects for funding, our aim was to map the views of different groups in a global barometer, and for this reason we employed a simpler process for prioritization. A potential limitation of our methodology was that international experts prepared the initial list of topics used in the prioritization survey, based on their understanding of the relevant literature, current practices, and unmet needs. Nevertheless, all respondents had the opportunity to suggest additional topics in every domain; only a few additional questions came up, suggesting that saturation was practically reached.

We did not capture potential conflicts of interest of the (>400) respondents to the prioritization exercise; however, given the large number of respondents from different stakeholder categories, we believe that the integrity of our findings is maintained. Moreover, responses from each stakeholder group are presented separately in Figures 2 to 5, and notable differences are discussed.

Another potential limitation of our survey was that it was available in scientific and plain English versions, but was not translated to other languages. Despite the global geographic

FIGURE 4. Number of participants considering a priority each of the unaddressed clinical questions on drug therapy, by stakeholder category. Prioritized topics appear in bold. For each question, the colors of the bars reflect the difference in the response rate of each respondent category from the overall median response rate.

FIGURE 5. Number of participants considering a priority each of the unaddressed clinical questions on nondrug management and other topics, by stakeholder category. Prioritized topics appear in bold. For each question, the colors of the bars reflect the difference in the response rate of each respondent category from the overall median response rate.
spread of the respondents, this could have limited the representation of non—English speaking people.

The major strength of our study is the inclusion and independent evaluation of the responses of representatives of 5 different stakeholder groups and 60 countries with different economies around the world. Although clinicians and researchers across Europe and the United States represented the majority of our sample, we had adequate responses from all responder groups and we were able to compare and contrast the responses across responder groups, which were generally homogeneous.

Ethical and regulatory constraints in conducting research in children, in combination with the relatively lenient criteria for extension of adult asthma drug licenses and nondrug treatment interventions to children, delay gathering of relevant data. However, given the crucial differences in the mechanisms and treatment requirements of different phenotypes of childhood asthma, compared with adult asthma, data extrapolated from adult studies cannot optimally support treatment decisions in children. Although conducting research in children can be criticized because it is not always without risks (similar as with adults), administering potentially harmful treatments before the benefits have been established in the relevant target group is not without risks either. Therefore, there is an urgent need to promote and facilitate clinical research in pediatric asthma globally and produce much-needed, high-quality, objective evidence. Of course, research involving children, which consist of a vulnerable population, should be regulated and adhere to good clinical practice guidelines. In parallel, evidence-informed recommendations focusing on children of different ages, with contributions by a wide range of stakeholders and considering the described unmet needs, should be developed. The prioritization of major unmet needs and—more importantly—the identified discrepancies in the perceived priorities among patients, clinicians, and other stakeholders, has crucial clinical implications. More specifically, they revealed unaddressed needs of children with asthma and their caregivers for more information, guidance, careful balancing of therapeutic risks and benefits, and—when appropriate—specialist involvement in the initial diagnosis of childhood asthma.

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N. G. Papadopoulos was involved in study conception. A. G. Mathioudakis and N. G. Papadopoulos were involved in study design and data analysis. All authors were involved in interpretation of the findings and critical revision of the manuscript.

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ONLINE REPOSITORY

METHODS: IDENTIFICATION OF POTENTIAL PARTICIPANTS

We conducted an extensive systematic review to identify experts and other stakeholders from across the globe, who have contributed to pediatric asthma research, innovation, and clinical recommendations during the last decade. To ensure global input, the survey was circulated to clinicians and researchers with relevant expertise by the Respiratory Effectiveness Group and the European Academy of Allergy and Clinical Immunology. In addition, it was circulated to caregivers of patients with pediatric asthma by the European Lung Foundation, the European Federation of Allergy and Airways Diseases Patients’ Associations, and the Global Allergy and Asthma Patient Platform. A database previously established in the context of an EU project (EARIP) was used to identify pharmaceutical industry and regulatory body representatives.

RESULTS: ADDITIONAL DETAILS ON THE PRIORITIZATION PROCESS

Identification of unmet clinical needs

Twenty-six international experts (93% of those invited) from 16 countries in 5 continents completed the initial, open-question survey, which aimed to capture important unanswered clinical questions in pediatric asthma. After removing duplication, the initial list of 489 questions was limited to 57 unique topics, which were classified into 4 categories: diagnosis, classification, and natural history (n = 13); drug therapy (n = 13); and nondrug management and other questions (n = 16). The full list of the questions is given below.

The survey identified a number of key topics that require attention, including mostly research but also strategic and policy issues. These included consensus on the definition, criteria for diagnosis, and classification of pediatric asthma, which may well differ among different age groups within childhood. Risk factors for asthma, biomarkers and phenotypes associated with disease severity, natural history, and responsiveness to treatment, as well as the characterization of clinical phenotypes, were also identified as unaddressed questions. Most importantly, responders highlighted the need for direct evidence from interventional, epidemiological, and mechanistic studies in children and evidence syntheses of such studies, to guide nonpharmacological and pharmacological management of persistent childhood asthma and exacerbations. Finally, environmental control, adherence to treatment, inhaler technique, telemonitoring, community school intervention, asthma prevention, and the role of early routine assessment of comorbidities were additional domains proposed for prioritization.

Prioritization of unmet clinical needs

The prioritization survey included the 57 questions that were previously identified. It was completed by 412 participants, from 60 countries in 5 continents (all but Antarctica, details in Figures E1 and E2). The precise response rate could not be calculated, because this survey was promoted via several independent routes, including social media. Clinicians and researchers, predominantly from Europe or America, were overrepresented in the sample. However, we received responses from all continents (except Antarctica) and responder groups, and we were able to compare trends and differences across the groups. Demographics of responders are available in Figure 1, and Figures E1 and E2. The number of questions that were included in each domain and the number of responses that participants were permitted to select are summarized in Table I.

CLINICAL QUESTIONS IN SCIENTIFIC ENGLISH

1. Diagnosis, classification, natural history
   Allergy as a classifier.
   Available diagnostic tests (lung function, fractional exhaled nitric oxide, airway hyperresponsiveness, questionnaires).
   Can available interventions prevent/influence disease progression?
   Comorbidities: should comorbidity classifications (eg, asthma-rhinitis) be considered?
   Evidence and clinical utility of an endotype/phenotype-based classification.
   How can we define/confirm/predict disease remission?
   Is there an optimal, evidence-based age grouping for asthma management?
   Minimum diagnostic criteria in different age groups.
   Prediction of fixed airway obstruction later in life. Is it possible?
   The optimal diagnostic pathway. Do we need different pathways depending on the phenotype?
   Tools/indices predicting asthma development/persistence from childhood to adulthood.
   What are the early risk factors for severe, uncontrolled asthma?
   What is the impact of ongoing stimuli (pollution, smoking, infection, etc.) on asthma natural history and outcomes?

2. Assessment and monitoring
   Age-specific assessment of asthma control.
   Age-specific assessment of asthma severity.
   Age-specific cutoffs for airway obstruction.
   Biomarkers (diagnostic, classification, prognostic, treatment response).
   Bronchial endoscopy/biopsy.
   Home lung function monitoring.
   How should we monitor asthma control? At what intervals?
   High resolution computed tomography in children with limited reversibility.
   Patient-reported outcomes.
   Safety monitoring (bone density, height).
   School monitoring.
   Systemic or airway inflammation monitoring.
   Telemonitoring and eDiaries.

3. Drug therapy
   Algorithms for choosing medications.
   Assessment of inhaler technique and adherence.
   Biologics place in treatment.
   Criteria for controller treatment initiation (age, severity).
   Criteria for stepping down.
   How can we prevent airway remodeling?
   Inhaled devices.
   Maintenance and reliever therapy and single maintenance and reliever therapy regimes in children.
   Medications available to children with asthma at different ages.
   Direct versus indirect evidence.
   Oral corticosteroids.
Therapeutic aims.
Written asthma management plan.

4. Nondrug management and other topics
Are there differences in asthma nature across different ethnicities?
Is there a role for educational programs?
Is there a role for e-health and m-health?
Is there a therapeutic role for allergen avoidance?
What is the role of community/family/school support?
What is the “cultural” meaning of asthma in different communities?
What is the prevalence and burden of pediatric asthma?
What is the role of balneo- and climatology, spa, sanatoria, etc.
What is the role of diet?
What is the role of exercise and physiotherapy?
What is the role of psychological support?
What is the role of smoking cessation programs for parents?
What is the role of supplements, probiotics, prebiotics, vitamins, etc.
What is the role of vaccination?
When and how to refer for allergy testing?
Who should be referred for specialist diagnostic assessment?

CLINICAL QUESTIONS IN PLAIN ENGLISH

1. Diagnosis, classification, natural history
Can we identify different subtypes of asthma in children that may require different treatments (so-called phenotypes or endotypes)?
Do we need a personalized approach to the diagnosis of asthma, in children with different asthma subtypes?
Do we need to treat differently children with coexisting allergy?
How can we predict the progression of asthma in adulthood and its future severity?
How can we predict whether asthma will have permanent effects in the lungs later in the life?
How does continuous exposure to pollution, smoking, infections, and other factors impact asthma progression and outcomes?
How important is it to assess for and treat other medical problems that children frequently have?
How should we group children by age, in order to deliver the most appropriate management?
In children not experiencing asthma symptoms any more, how can we confirm that asthma is in remission?
Using available treatments, can we prevent the long-term impact of asthma on children’s health?
What factors cause or predict the development of severe, very symptomatic asthma?
What is the simpler way to confidently diagnose asthma in children?
Which are the most accurate diagnostic tests?

2. Assessment and monitoring
Home lung function monitoring.
How can we accurately interpret patients’ descriptions of their disease and symptoms?
How can we evaluate asthma control in different age groups?
How can we evaluate asthma severity in different age groups?
How should we monitor asthma control? At what intervals?
High resolution computed tomography (detailed lung scans) in children with limited reversibility.
Safety monitoring (height, osteoporosis monitoring).
School monitoring.
Systemic or airway inflammation monitoring.
Telemonitoring and e-Diaries.
What are the cut-point values that reveal abnormal results in breathing tests in different age groups?
What blood tests (biomarkers) provide important information about the diagnosis management and future risk of deterioration in childhood asthma?
What is the role of bronchoscopy (camera test looking in the lungs) and of receiving tissue samples in childhood asthma?

3. Drug therapy
Asthma treatments have side effects. When should we consider stopping some of the treatments children receive for their asthma (because they may not need them anymore)?
Can some children be managed only with biologic treatments?
Development of simple algorithms to standardize and improve the management of asthma in children.
How can we assess whether children are using their inhalers correctly and regularly? (By not doing so, they are not getting adequate treatment).
How can we decide whether children require regular treatment for their asthma? (How severe disease? What age?)
How can we deliver personalized treatments for people with different asthma subtypes (phenotypes and endotypes)?
How can we prevent the permanent damage that asthma may cause to the airways?
Many children have only 1 inhaled medication to use regularly, but also as a rescue treatment when they experience increased symptoms. What direct evidence from children studies supports this approach?
What advise should we give to children and their parents regarding how to manage increased asthma symptoms themselves, before having to see a doctor?
What evidence supports the use of different medications in children of different ages? (Direct evidence from children studies, in contrast with indirect evidence from studies in adults, which may not have the same response to some medications).
What is the most effective and simple to use in the children inhaler device?
What is the role of immunotherapy in children with asthma? Immunotherapy is proved to be effective in some cases, but is also associated with side effects.
What is the role of the regular use of steroid tablets?
What is the role of strong biologic treatments (which however may have side effects) in the treatment of children with asthma? (How severe disease? What age?)
When should we really consider them?
What should clinicians aim for when treating children with asthma?

4. Nondrug management and other topics
Does the presentation and management of asthma vary based on ethnicity?
What is the “cultural” meaning of asthma in different communities?
What is the frequency of childhood asthma and what burden does it cause to patients and the society?
What is the role of avoidance of allergens in asthma management?
What is the role of balneo- and climatotherapy (spa, sanatoria, etc.) in asthma management?
What is the role of community support (family, school, etc.) in asthma management?
What is the role of diet in asthma management?
What is the role of educational programs in asthma management?
What is the role of e-health (electronic) and m-health (mobile phones) in asthma management?
What is the role of exercise and physiotherapy in asthma management?
What is the role of nutritional supplements (probiotics, prebiotics, symbiotics, bacterial lysates, antioxidants, vitamins, etc.) in asthma management?
What is the role of psychological support/treatment in asthma management?
What is the role of smoking cessation programs for parents in asthma management?
What is the role of vaccination in asthma management?
When and how to refer for allergy testing?
Who should be referred for specialist diagnostic assessment?

OTHER SUGGESTED UNADDRESSED QUESTIONS

1. Diagnosis
Accurate severity scoring for acute exacerbations.
Impact of E-cigarettes on asthma and lung function development
Can we improve adherence and how does this influence asthma control?
Does an early diagnosis influence disease progression/outcomes?
Tests (lung function, auscultation, questionnaires) to early detect exacerbations

2. Assessment
Which are children preferences/wishes or parental preferences/wishes when two options are presented in a BRAN (benefits, risks, alternative, nothing) decision aid tool?
Medication adherence.
Behavioral aspects of noncompliance.
Measurement of pulmonary functions in young children.

3. Monitoring
Are there differences in phenotype, biomarker profile, and clinical presentation as well as response to treatment between children with severe/uncontrolled asthma and adults with severe uncontrolled asthma.
Role of electronic medication monitoring in clinical practice.
Is it ethical to medicalize children by monitoring them?
Who do we best integrate symptoms and physiological measurements when assessing asthma control?

Development of the “omics” approach to rational treatments: possibly urine metabolomics coupled to endotypes

4. Drug therapy
Should intermittent therapy with inhaled corticosteroids be the gold standard?
Impact of health insurance policies on medication.
Effective “as needed” therapy short of oral steroids.
Decision aid tools for including children and parents’ preferences and wishes, anxiety and expectations.
Do cognitive and emotional development of children and adolescents with asthma depend on type of pharmacotherapy they use?
Is montelukast effective? If yes, which patients benefit from montelukast?
Use of short acting beta-2 agonists immediately post discharge (regular reduction or as needed in children).
Effects of leukotriene receptor antagonists on systemic inflammation.

5. Nondrug therapy
Medications adherence.
National or regional asthma programs.
Place of vitamin D particularly.
Parenting intervention/support to improve adherence to treatment.
Impact and management of social determinants of health in asthma care.
Allergen specific immunotherapy
Environmental pollution—what thresholds actually relate to increased disease severity?
Medications adherence.
What is the role of hypertonic solutions?
How does time spent outdoors affect disease control and progression?
What is the role of breathing therapies?
What is the role of pranayama and yoga?
Effective allergen elimination (eg, Airsonett).
Outdoor and indoor air pollution interventions.
Breathing techniques (for dysfunctional breathing).
Is there a role for manipulation of the airways microbiome?
What is the role of essential oils?
How asthma influences patients’ life routine?
Prenatal influences and early prevention
How to strengthen a compliance and a positive therapy outcome?
How to modify a social perception toward patients with pediatric asthma?
How to strengthen a positive social image of patients with asthma and their families?
FIGURE E1. Responders by country of practice.
FIGURE E2. Number of respondents by country of practice of the respondents.
FIGURE E3. Number of participants considering a priority each of the unaddressed clinical questions, by economy. (A) Diagnosis, classification and natural history. (B) Assessment and monitoring. (C) Drug therapy. (D) Non-drug management and other topics.
FIGURE E3. (CONTINUED).

What is the role of oral corticosteroids? Which should be the therapeutic aims? What is the correct inhaler device for every child? What is the role of written asthma management plan? Can we manage some children with biologics only? How should we assess inhaler technique and adherence? Criteria for controller treatment initiation according to age and severity. What direct evidence is there for use of medications at different ages? What is the role of MART and SMART regimes? What is the role of biologics? Algorithms for choosing medications What is the role of immunotherapy in treatment? Criteria for stepping down treatment. How can we prevent airway remodeling? Endotype/phenotype/biomarker driven treatment.

What is the role of balneo- and climatotherapy, spa, sanatoria etc. What is the role of vaccination? Is there a role for e-health and m-health? What is the role of community/family/school support? What is the role of diet? What is the role of psychological support? Is there a role for educational programmes? What is the role of smoking cessation programmes for parents? Is there a therapeutic role for allergen avoidance? What is the role of exercise and physiotherapy? What is the “cultural” meaning of asthma in different communities? What is the prevalence and burden of paediatric asthma? When and how to refer for allergy testing? Who should be referred for specialist diagnostic assessment? Are there differences in asthma nature across different ethnicities? What is the role of supplements, probiotics, prebiotics, vitamins etc?
FIGURE E4. Number of participants considering a priority each of the unaddressed clinical questions, by continent. (A) Diagnosis, classification and natural history. (B) Assessment and monitoring. (C) Drug therapy. (D) Non-drug management and other topics.
FIGURE E4. (CONTINUED).

REFERENCE