These responses were compiled by Dr. Szefler with assistance from the authors of the publication on “Asthma Across the Ages: Knowledge Gaps in Childhood Asthma”

Natural History and Pathophysiology:

1. What of new classes of drug not included in the 4 categories?

   **Response:** There are several new drugs that are being developed for the treatment of asthma including tiotropium and new immunomodulators. These drugs will have to be studied according to new regulations proposed by the United States Food and Drug Administration (FDA) as well as other regulatory agencies.

2. With regard to the discussion of genetics and the inception of asthma, what role does race (and ethnicity) play, independent of environmental co-variables?

   **Response:** This is an excellent question. Clearly race is an independent risk factor for the onset and severity of asthma. It is difficult to disentangle the environmental from the genetic co-variables. Results from some of the large on-going GWAS meta-analyses will be helpful in evaluating this.

3. With regard to the role of sex (or sex hormones) and genetics in airway pathophysiology and for disease prevalence, what is interesting to recall and consider the significance of is RDS where premature white male infants are at the greatest risk.

   **Response:** Thank you for this comment. It is indeed interesting that white males are more at risk for RDS and that the incidence of asthma is greater in males before puberty and in females after puberty.

4. How to measure outcomes in the trials where there is no established MCID or where the drug is an add-on therapy to measure add-on efficacy and relative merit/value?

   **Response:** This question highlights why it is important to continue the development of patient centered outcomes and validate them in clinical trials.

5. If pediatric asthma is not the same as adult asthma and in development trials efficacy must be documented in addition to safety and PK for ever decreasing age groups, what should be the efficacy measure used?

   **Response:** The FDA has consistently used FEV1 as a preferred outcome measure in interventional trials, but seems to be more willing to evaluate alternative outcomes. Therefore, there is a need to develop novel indicators including biomarkers that evaluate the efficacy of a drug on its intended target. For example, exacerbations (frequency and time to exacerbation) would be important in a trial evaluating a drug used to prevent an acute asthma exacerbation.

6. What of PROs and other symptom measures in pediatrics?

   **Response:** Patient reported outcomes are being more accepted by the FDA for use in clinical trials because they document the impact of interventions on activities of daily living and other factors relevant to patients and families.

7. For discussions of airway remodeling in children and comparisons with adults, what consideration has been made for normal growth, variations of normal, and also contributions from other antecedent processes (eg prematurity) which may have nothing to do with asthma at all?
Prematurity was an exclusion criterion in these studies. Knowing the impact of variation in normal development on airway remodeling is an important issue. However, studies to determine this would be difficult to undertake because such studies would require large numbers of participants, and there are ethical concerns with performing biopsies in young healthy children.

8. “Does the severity of the exacerbation matter?” Which guidelines and/or definitions are used here? The most recent ATS/ERS guidance moved away from severities for exacerbations.

Response: This is a question we asked in the manuscript. We do not understand the long-term impact of exacerbations including whether severity is important to long-term outcomes. In reviewing the guidance from the ATS and ERS published in 2009 (Reddel et al, AJRCCM), it was noted that defining severe versus moderate exacerbations might be helpful for standardizing outcomes for clinical trials.

Diagnostics and Biomarkers:

1. Without established accepted measures of lung function or acceptable proxy-measures for use in a clinical trial, if a trial were conducted using oscillometry and were positive, for example, how would this translate to indication/labelling and extend to the prescribing physician?

Response: IOS appears to have similar, if not better, differentiation of lung function than standard spirometry and can be reliably used in the preschool population. In the absence of standardized measurements, repeated oscillometry may be used to show medication effect on the small airways as a significant change in reactance. If this change in airways function was significantly different in the treated versus untreated group it would be a functional marker of a biologic event, similar to how spirometry is used. Determination of its value in the context of the signs, symptoms and morbidity of disease still needs to be worked out, but early data suggests that it may be correlated with future morbidity.

In other words, some functional marker of airways disease is better than none particularly in the preschool age range, where spirometry is difficult to obtain and FEV1 is often a poor measure in children. There is some data that IOS has some data that it is more sensitive.

REFERENCES:

2. Discussion focused on role of biomarkers in disease progression what about for questions of maintenance/control?

Response: The Severe Asthma Research Program1 identified FeNO as a marker of adherence, suggesting control by improving inflammation through maintenance anti-inflammatory medications. Ample data suggests that management by FeNO encourages over treatment2, compared with guideline based therapy, suggesting further understanding is an unmet need, particularly in children.

REFERENCES:

3. “Specific biomarkers of disease and disease progression are needed but are lacking in children” is cited as an unmet need, and while this is likely to be true, given that evidence is weak or lacking in this area for adults, should this be taken into consideration when prioritizing the identified and suggested area of need?

Response: If this comment suggests unmet need in children should be prioritized lower than adults then the answer is NO. Finding these markers in children when asthma is first developing and likely to be either at early stages or at least un-confounded with other risk factors such as tobacco smoke, occupational exposure, etc, is likely more important than in adults. The identification of these markers in children may make for substantial gains in halting or mitigating the disease process in its nascence. However, if this comment is implying that it should be considered for both populations, adults and kids, then agree, that understanding biomarkers across the ages is indeed an unmet research need.

Outcome Measures:

1. While the recommendation to include as an outcome measure exacerbations in all trials is understandable, the reality of the study design and execution becomes extremely challenging and if powering a study with exacerbations as the primary outcome measure, the number of patients necessary becomes impossible.

Response: Agree. The NHLBI Task Force recommendations were not mandates. Rather, the document was intended to serve as guidance to investigators designing studies with exacerbations as an end point. “Exacerbation” is indeed a soft outcome, so the document intended to standardize the approach for how an exacerbation should be defined. With regard to power for studies, composite measures are more likely to reflect the heterogeneous nature of asthma. Also, patient-oriented outcomes and exacerbations (as one example) are much more meaningful to patients than FEV1.

2. How to incorporate variability in FEV1 (both inter-patient and intra-patient) over an age-range for trial design and to evaluate results.

Response: This is an ongoing challenge. The best approach is one that focuses on percent predicted values as opposed to absolute values given the dynamic nature of lung growth in children. Other important issues with FEV1 are: 1) the crude nature of the measure (i.e., it reflects mostly large airways as opposed to small airways which may be more relevant) and 2) the limitations with percent predicted equations which assume purity of racial background and ignore admixturing (this results in a measurement problem for multi-racial individuals). There is indeed a high degree of maneuver-to-maneuver variability in the FEV1 measure (up to 10%) so small changes below this may be clinically irrelevant. There is also a great deal of controversy regarding pre- versus post-bronchodilator measures. To this point, there is no evidence that any existing asthma treatment (including ICS) modifies the natural history of lung function decline (i.e., post-bronchodilator FEV1). However there is some evidence that asthma therapies improve pre-bronchodilator FEV1 on a short-term basis.

The field needs are more sensitive measures of airway caliber and tone irrespective of height, racial background and other variables. These measures ultimately need to reflect the ventilation heterogeneity in the airways since accumulating evidence suggests that the airway defects in asthma are not homogenous throughout the airway tree.

3. The need to further characterize drug delivery and distribution is suggested for inhaled therapies, however, how great is the need for new drug development in this area at this time? (ie new drug development in asthma seems currently focused on injectables and oral therapies.)

Response: Despite the growing interest in biologics, 90% of patients with asthma can be well controlled with traditional ICS therapies assuming that other factors (co-morbid conditions, exposures, adherence and access to care) have been appropriately addressed. Better delivery and distribution could ultimately result in less systemic toxicity since smaller cumulative doses of ICS could be achieved. Also, while biologics are certainly necessary for severe asthma that is unresponsive to ICS therapy, this strategy is not fiscally appropriate for most patients given that nearly 1 out of 10 individuals in the US has asthma.

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Therapeutics:

1. “Identify the studies that should be conducted to appropriately label medications for the management of acute asthma exacerbations in children” is identified as an unmet need, however, there must be agreement with regulatory agencies for details of endpoints, what is considered a clinically meaningful result, and for adaptive trial design.

   **Response:** The following publication addresses this question: Asthma outcomes: Exacerbations; (J Allergy Clin Immunol 2012;129:S34-48.)

   “Recommended definition: An exacerbation is a worsening of asthma requiring the use of systemic corticosteroids (or for patients on a stable maintenance dose, an increase in the use of systemic corticosteroids) to prevent a serious outcome. This definition is the same for pediatric (aged 0-4 and 5-11 years) as for adult and adolescent populations. Although the use of SABAs is a more commonly used criterion or factor for defining “exacerbation” in children, the threshold criterion for distinguishing between loss of control and an asthma exacerbation has not been defined. Therefore this criterion could not be included as a core outcome.”

2. “Identify the age-appropriate inhaled drug administration technique that provides optimal lung delivery of medications” is identified as an unmet need, yet for inhaled drugs no correlation exists between studies of drug deposition and corresponding effects upon lung function.

   **Response:** Optimal lung delivery can be translated to clinical effect. We were questioning use of MDI+facemask compared to budesonide nebulizer solution at equivalent doses.

3. What consideration to cost in the discussion of unmet needs? Cost for the patient for a prescription therapy (or two or three) for the physician visit to administer said therapy, and also for the sponsor to conduct the trials to get said therapies to the market?

   **Response:** The reviewer has identified ALL THE COSTS! The cost of medication is a concern as much as the time spent to instruct and educate the patients how to use the inhalers/nebulizers.

Other questions:

1. The task of the Asthma Working group was to discuss the main areas between childhood and adult pediatric asthma to define specific knowledge gaps related to current asthma management. Was safety included as a specific consideration for each of the two broad issues (ie drug delivery and outcomes measures)?

   **Response:** Yes, besides efficacy, safety is always a major consideration, especially when it comes to children. In general, the younger the child, the more important it is to consider unique effects on growth and development.

2. Were there differences within the category of pediatrics between age groups (ie adolescents, school-age children, and young children) for the findings of the review?

   **Response:** That is a very good comment and it was addressed in the panel discussion following the webinar presentation.

3. Asthma is the perfect example of a disease that has diverse clinical presentations depending upon the patients’ genotype and environmental exposures. With that in mind and the possible entrance of a number of biologic treatment options for asthma, please detail the role you feel biologics such as the IL-5 inhibitors and others may play in the treatment of asthma.

   **Response:** That is an important comment. These drugs are at a very early stage. With some promising results, especially when linked with biomarkers that appear to be associated with a positive response, there will be continued drug development efforts and will subsequently be tested in various age groups, as efficacy and safety are demonstrated. It appears that these drugs will be linked to a biomarker that is associated with a positive response. Response may also vary with the drug. Some may have an effect on exacerbations while others may have an effect on symptom control without a dominant effect on exacerbations and vice versa.

4. Do you feel these drugs will play a role in disease modification?
Szefler: If this question is in reference to the new immunomodulator therapies, they do have that potential but they need to be adequately evaluated.

5. In the Biomarker section under FeNO, we would suggest adding a sentence that says 'recent studies have suggested that using FeNO to guide anti-inflammatory therapy in asthma results in reduced exacerbations in children.' (Piersman 2013, Mahr 2013) Both papers suggest up to a 50% reduction in asthma exacerbations when therapy is guided by the use of FeNO versus standard of care. References are below:


Response: Thank you for this suggestion. The summary has already been published in the January 2014 issue of the Journal of Allergy and Clinical Immunology. If there is an opportunity for follow-up comments, we will consider adding this information.

6. It would be nice to tie in discussion points, when appropriate, with the publication of 'An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice'; Reddel et al 2009. This probably would be most relevant with respect to the section on outcome measure. Obviously the ATS/ERS document only provides recommendations for patients 6 years and older.

Response: Indeed, the publication mentioned above was a starting point and was followed up with an NIH Asthma Outcomes Task Force that was published in the Journal of Allergy and Clinical Immunology in March 2012.

7. Small point: I accept that this paper has a large U.S. focus, none the less, it is worth noting that on page 7 it states that omalizumab is licensed in patients 12 years and above. In Europe, it is licensed for patients 6 years and above.

Response: Yes, this difference was mentioned on the Webinar.