A. SPECIFIC AIMS. Despite the widespread availability of asthma controller medications such as inhaled corticosteroids **(ICS)** in the United States, asthma control in children <18 years remains suboptimal and nearly 50% of affected children experience a significant asthma exacerbation each year.[1] While the factors responsible for exacerbations are complex and include access to care and treatment compliance,[2] there is also growing recognition that children with asthma are a heterogeneous group, with many underlying biologies or "endotypes" that contribute to differing phenotypic disease presentations, differential responses to ICS treatment, and varied clinical outcomes.[3-9] However, compared to adults, phenotypic characterization of children with asthma is quite limited and is not currently performed in the clinical setting. Early identification of children with asthma who are at risk for poor outcomes (namely exacerbations) is therefore one of the primary challenges faced by clinicians who provide care to these children. As a result, the clinical course of children with asthma is often an enigma that is difficult to predict; there is also limited evidence to guide pharmacotherapy and a sizeable knowledge gap.

This study will leverage existing data from a cohort of >2,500 well-characterized children age 5 up to 18 years with persistent asthma enrolled in NIH/NHLBI clinical trials (data custodian Dr. David Mauger, co-Investigator) to test the overarching hypothesis that **phenotypic and associated endotypic features predict exacerbations, symptom-free days (SFDs) and the response to ICS treatment in children with persistent asthma**. We will test two aims in this pilot; Aim 3 will leverage available biospecimens from these children and will be pursued in a future grant application. This analysis builds upon 10 years of collaborative work including 12 joint publications and 2 additional manuscripts in peer review (see Biosketches).This work is also a crucial step toward our mutual goal of advancing personalized medicine for children with asthma.

- **Aim 1. Identify and characterize asthma phenotypes in children with persistent asthma.** Hypothesis: A phenotype distinguished by underlying Type 2 (i.e., Th-2) eosinophilic-mediated inflammation will be identified by latent class analysis **(LCA)** and will be associated with a greater magnitude of current symptoms and greater prior healthcare utilization for asthma in cross-sectional analyses.
- **Aim 2. Determine whether asthma phenotype/endotypes are associated with poor asthma outcomes.** Hypothesis: The phenotype with Type 2 inflammatory features will have a higher annualized rate of exacerbation (primary outcome) and fewer SFDs (secondary outcome) while treated with placebo, but a more robust response (i.e., fewer exacerbations, more SFDs) to ICS treatment initiation (exploratory outcome).
- **Aim 3. (Future grant application). Refine prediction models for asthma exacerbations, SFDs and ICS treatment responses with other endotypic features (cytokines, metabolomics, immune cell studies).** Hypothesis: Identified phenotypes will have distinguishing cytokine profiles, plasma metabolomic biomarkers and circulating immune cell functions that associate with exacerbations, symptoms and ICS treatment responses.

B. SIGNIFICANCE. Asthma currently affects 8-10% of all children in the United States.[10-12] Morbidity from acute exacerbations of asthma in children is highly significant, and in rare cases, results in death.[13] Asthma exacerbations in children also contribute to missed school/work days,[14, 15] impaired caregiver functional status,[16] and a growing personal[17] and societal[18] economic burden estimated at >$80 billion annually.[19] Although there are mandates for "personalized" versus "one-size-fits-all" treatment of children with asthma,[20] there are challenges that must be overcome. Major barriers include inadequacies of animal models in recapitulating human disease and differences in human developmental stages that prohibit extrapolation of knowledge from adults to children. Indeed, Dr. Fitzpatrick recently participated in NHLBI[21] and NICHD[22] Working Groups focused on gaps in understanding of asthma. The primary theme that emerged from both groups was the need for additional studies in children, namely those that: 1) identify phenotypes and endotypes to advance personalized medicine, and 2) evaluate alternative methods to predict heterogeneity in the response to treatment. This study seeks to fill these critical knowledge voids to ultimately improve the public health of this prevalent disorder. This study also builds on 10 years of collaborative work on childhood asthma (see Biosketches).

INNOVATION. This proposal leverages a unique cohort and involves novel ideas and analyses that have not previously been undertaken in asthmatic children in the United States. First, our cohort spans the disease severity spectrum and is the first to be fully characterized with regard to atopy/sensitization, reversibility of airflow obstruction, medical history, environmental exposure, medication adherence, ICS and systemic corticosteroid treatment responses, and genetics. Second, this would be the first study to utilize a novel statistical technique in medical research, latent class analysis **(LCA)**, to identify phenotypes of childhood asthma in the United States. These phenotypes clearly differ from phenotypes identified in Europe and other regions where exposures and risk factors differ. Third, in other observationalcohorts, inconsistencies in the definition of "exacerbation"[23] and variable prescription of (and adherence to) asthma controller medications such ICS complicate outcome assessment. This would be the first study to assess asthma exacerbations in a standardized way, with consideration of medication treatment effects. The results therefore have the potential to inform future phenotype-guided interventional studies.

C. APPROACH. Rationale. As recently stated by Francis Collins, "the success of personalized medicine depends on having accurate identification of patients who can benefit from targeted therapies."[24] However, segmentation of children with asthma into distinct phenotypes (*i.e., patient groups with similar clinical features*) and endotypes (*i.e., biological mechanisms within phenotypes*) is a primary challenge in pediatric airway research[22] and is not currently performed in the clinical setting. This is in contrast to adults with asthma, in whom phenotypic/endotypic characterization has been described for the purpose of biological drugs such as anti-IL-5.[22]

Preliminary data. We previously performed a LCA of 5 NIH/NHLBI clinical trials involving 1,708 preschool participants age 12-71 months with recurrent wheezing (manuscript in review by the *Journal of Allergy and Clinical Immunology*). Details of the included studies (i.e., Prevention of Early Asthma in Kids (**PEAK,** NCT00272441),[25] Acute Intermittent Management Strategies (**AIMS,** NCT00319488),[26] Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (**MIST**, NCT00675584**)**,[27] Azithromycin for Preventing the Development of Upper Respiratory Tract Illnesses into Lower Respiratory Tract Symptoms **(APRIL,** NCT01272635**)**,[28] and Individualized Therapy for Asthma in Toddlers **(INFANT,** NCT01606306)[8] were published previously. Data were used from the total sample of 1,708 participants at the baseline and randomization visits. LCA was performed on 10 variables to determine the optimal number of latent classes: 1) sex, 2) parent with asthma, 3) tobacco smoke exposure (any smoker in any household in which the participant regularly spends time), 4) eczema (ever), 5) indoor pet ownership (defined as a cat or dog inside the home), 6) race/ethnicity (non-Hispanic black/non-Hispanic white/Hispanic/other), 7) aeroallergen sensitization (none, 1-3, or ≥4 positive tests), 8) food sensitization (none, 1-2, or 3 positive tests), 9) blood eosinophil percentage quartile, and 10) serum IgE quartile.

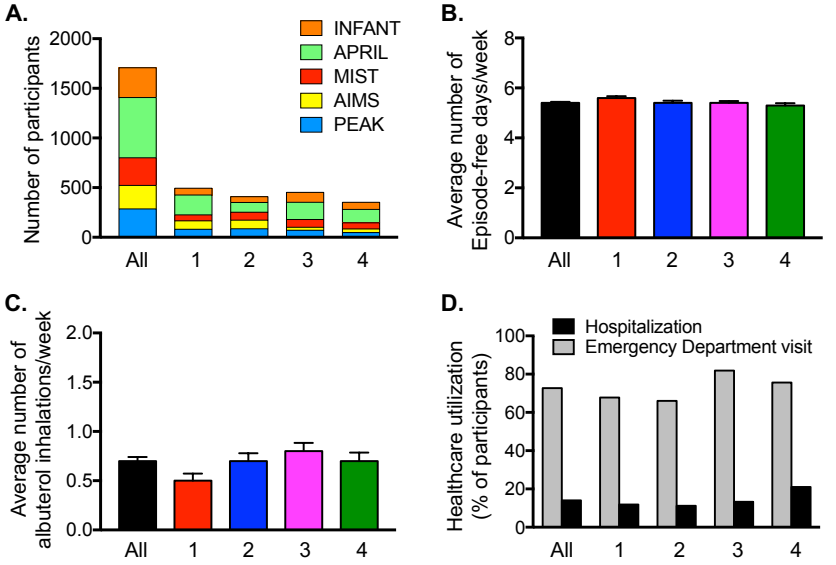

Figure 1. A) Distribution of studies, (B) symptom (episode)-free days and (C) albuterol inhalations during the study run-in periods (mean ± SEM), and (D) prior year healthcare utilization in all participants (N=1708) and each phenotype (1 = minimal sensitization [N=494], 2 = sensitization with indoor pets [N=409], 3 = sensitization with tobacco smoke exposure [N=452], 4 = multiple sensitization with eczema [N=353]).

Four phenotypes were identified: Phenotype 1 had minimal sensitization, Phenotype 2 had sensitization with indoor pets, Phenotype 3 had sensitization with indoor tobacco smoke exposure, and Phenotype 4 had

multiple sensitization and eczema. These groups were not differentiated by current symptoms or historical healthcare utilization over the preceding year **(Fig.1)**, but differed significantly with regard to the prospective annualized rate of exacerbations **(Fig. 2A)**. Over two years, the probability of exacerbation was greatest in both children with sensitization and indoor pet exposure (phenotype 2) and children with multiple sensitization and eczema (phenotype 4) **(Fig. 2B).** To determine the potential impact of daily ICS treatment on exacerbation rates, an exploratory analysis was performed on participants in the PEAK study (both placebo and ICS treatment arms). Daily ICS treatment was associated with a significantly lower exacerbation rate in children with sensitization and indoor pet exposure (phenotype 2) and children with multiple sensitization and eczema (phenotype 4), but not in children with minimal sensitization (phenotype 1) or children with sensitization and indoor tobacco smoke exposure (phenotype 3). Exacerbation rates did not differ between phenotypes after daily ICS treatment **(Fig. 3A).** Daily ICS treatment also significantly lowered the exacerbation probability in children with sensitization and indoor pet exposure (phenotype 2; Log-rank $X^2 = 9.226$; p = 0.002) and children with multiple sensitization and eczema (phenotype 4; Log-rank $X^2 = 4.710$; p = 0.030) **(Fig. 3B). These results provide additional insight on phenotypes of wheezing in preschool children and their potential utility with regard to key outcomes (exacerbations).** Furthermore, sensitization and indoor pet and tobacco smoke exposure assessment were also useful in the prediction of future morbidity and may identify those children most likely to respond favorably to daily ICS.

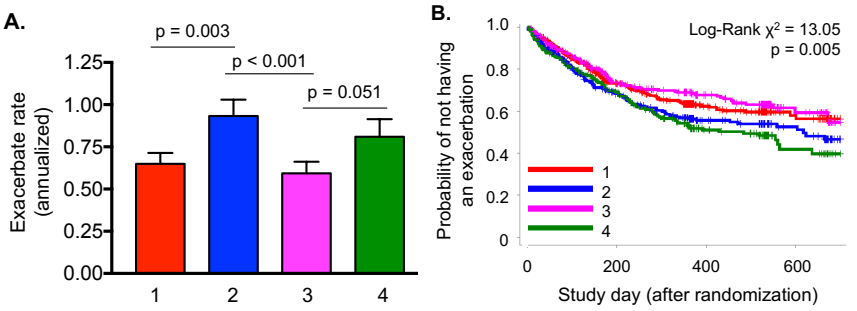

Figure 2. (A) Annualized rate (mean ± SEM) and (B) probability of exacerbation in placebo-treated children with minimal sensitization (phenotype 1, N=151), sensitization with indoor pets (phenotype 2, N=104), sensitization with tobacco smoke exposure (phenotype 3, N=132), and multiple sensitization with eczema (phenotype 4, N=102) in the PEAK/AIMS/APRIL studies. Numbers correspond to phenotype groups.

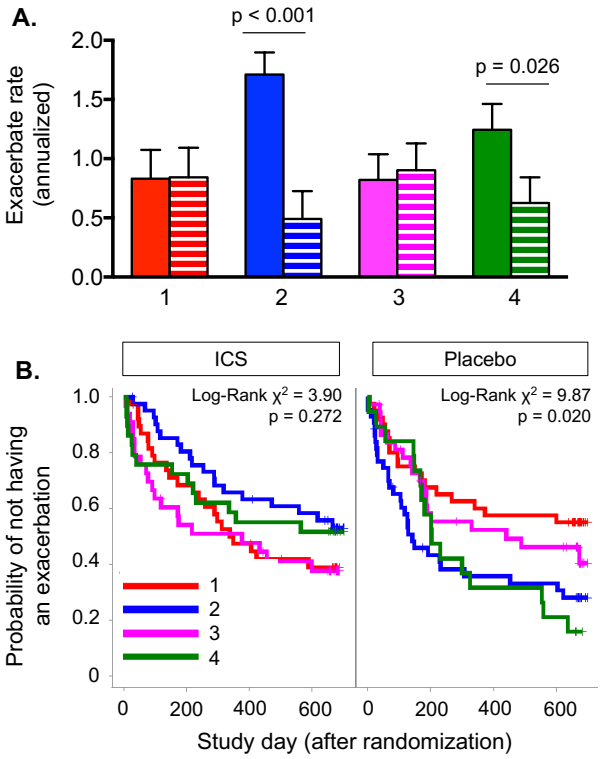

Figure 3. (A) Annualized rate (mean ± SEM) and (B) probability of exacerbation in the PEAK study placebo (solid bar) and daily ICS (hatched bar) treatment arms. Numbers correspond to phenotype groups (1 = minimal sensitization [N=41], 2 = sensitization with indoor pets [N=44], 3 = sensitization with tobacco smoke exposure [N=38], 4=multiple sensitization with eczema [N=19]).

Overview. We will perform a LCA of 8 NIH/NHLBI clinical trials involving 2,587 children age 5 up to 18 years with persistent asthma: The Childhood Asthma Management Research Program (**CAMP**, NCT00000575),[29, 30] Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (**CLIC**, no NCT),[31-33] Pediatric Asthma Controller Trial (**PACT**, NCT00272506),[34, 35] Montelukast or Azithromycin for Reduction of Inhaled Corticosteroids in Childhood Asthma (**MARS**, NCT00471809),[36] Best Add-on Therapy Giving Effective Response (**BADGER**, NCT00395304),[9, 37] Treating Children to Prevent Exacerbations of Asthma (**TREXA**, NCT00394329),[38] Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations

(**STICS**, NCT02066129),[39] and Best African American Response to Asthma Drugs (**BARD**, NCT01967173, to be published summer 2018). Details are listed in **Table 1**.

Study name	Years conducted	Number enrolled	Age (years)	Study design	Run-in period	Run-in medication	Treatment arm interventions	Arm Duration
CAMP[29, 30]	1993-1995	1041	5-12	Parallel	6 weeks	Placebo	Placebo vs. ICS vs. Nedocromil	4-5 years
CLIC[31-33]	2001-2002	144	6-18	Crossover	5-10 days	Placebo	ICS vs. LTRA	16 weeks
PACT[34, 35]	2002-2004	285	6-14	Parallel	2-4 weeks	Placebo	ICS vs. ICS/LABA vs. LTRA	48 weeks
MARS[36]	2006-2007	55	6-18	Parallel	2-4 weeks	ICS/LABA	ICS/LABA (+/- Azithromycin or LTRA)	24 weeks
BADGER[9, 37]	2007-2008	182	6-17	Crossover	2-8 weeks	ICS	ICS vs. ICS/LABA vs. ICS/LTRA	16 weeks
TREXA[38]	2007-2009	288	5-18	Parallel	4 weeks	ICS	ICS (+/- rescue ICS) vs. Placebo (+/- rescue ICS)	44 weeks
STICS[39]	2014-2017	254	5-11	Parallel	4 weeks	ICS	ICS (+/- rescue ICS)	48 weeks
BARD	2014-2017	338	5-17	Crossover	2-10 weeks	ICS	ICS vs. ICS/LABA	14 weeks

Table 1. Included studies. ICS = inhaled corticosteroid, LABA = long-acting beta agonist, LTRA = leukotriene receptor antagonist

Quality control. All studies were conducted by NHLBI-funded clinical research networks, overseen by dedicated Quality Control Committees and Data Coordinating Centers and utilized similar intake questionnaires. Paper case report forms were entered electronically and mailed to the Data Coordinating Center for review and accuracy upon completion. Each center maintained staff and site certification and utilized the same manual of procedures for characterization.

Participants. Written informed consent was obtained from all caregivers for trial participation and secondary data analyses. Exclusion criteria for each of the studies included premature birth, other significant respiratory conditions or recent antibiotic or systemic corticosteroid use within the previous 2-4 weeks. At the baseline visit of each trial, caregivers completed questionnaires to elicit data on demographics, family history, child allergy and respiratory symptoms, and treatment of symptoms including medications and healthcare utilization. SFDs were obtained during the run-in period from caregiver-completed diaries and were defined as full calendar days without use of albuterol, daytime or nighttime respiratory symptoms, or unscheduled healthcare visits for respiratory symptoms. Compliance with the diaries was used to estimate adherence and willingness to participate in the study; participants with unacceptable adherence (<75-80%) were ineligible for randomization. Peripheral blood eosinophils were quantified from whole blood by means of an automated assay at each clinical site. Total serum IgE was quantified centrally (St. Louis Children's Hospital or National Jewish Health). Skin testing or specific-IgE testing was performed with 8 common aeroallergens and 3 foods: dust mite (*D. pteronyssinus, D. farinae*), cockroach (*Blatella germanica*), dog, cat, mold (mix), grass (mix), tree (mix) weed (mix), cow's milk, chicken and whole egg, and peanut.

Outcomes. The primary outcome is the annualized rate of exacerbation during the study intervention period. The definition of exacerbation to be used was proposed by an NIH Working Group[23] and is defined as escalation of symptoms resulting in treatment with systemic corticosteroids (prednisolone). Secondary and exploratory outcomes will focus on SFDs and the effect of ICS treatment on exacerbations and SFDs within the phenotype groups. Intervention period data were collected over a 24-year period. For each study, irrespective of treatment allocation, caregivers received a written action plan that detailed instructions for administration of open-label albuterol sulfate (90 mcg/actuation) when a pre-specified threshold of symptoms was met. The action plan was reviewed and reinforced at each clinic visit. Children whose symptoms did not resolve or who required albuterol treatments for more than 24 hours received a 4-day burst of open-label oral prednisolone (2 mg/kg/day for 2 days followed by 1 mg/kg/day for 2 days) as specified in the action plan. Physician discretion for prednisolone administration was also permitted provided that a specific reason for the initiation was documented. Two courses of systemic corticosteroids had to be separated by at least one week to count as two exacerbations.

Aim 1: Phenotyping. All analyses will be performed with SAS software (version 9.4). Data missing completely at random and affecting <5% of participants will be subjected to multiple imputation to retain participants in the analysis. Other self-reported variables with missing responses or responses recorded as "don't know" will be recoded as "no." To limit the number of parameters in the model, variables will be selected based on clinical relevance and consistency across the studies. We will attempt to use the same 10 variables as those used in our previous LCA of preschool children (see preliminary data). LCA will be performed on all children in **Table 1** (N = 2,587) to identify phenotype groups using the PROC LCA procedure.[40] Conditional probabilities (probability of selected characteristics within a class) and posterior probabilities (probability of latent class membership for each participant) will be calculated. Models will be freely estimated with no specified parameter restrictions. Best fit will be assessed by comparison of the bootstrapped p-values for the likelihood ratio test and the Bayesian information criterion test. Each participant will be assigned to the phenotype with the highest membership probability.

Aim 2: Outcome analyses. The annualized rate of exacerbations (primary outcome), SFDs (secondary outcome) and ICS treatment effects (exploratory outcome) will be assessed in the placebo arms of the CAMP and TREXA studies (N = 1,329) to eliminate potential confounding effects of asthma controller medications such as ICS. Phenotype groups will be compared with respect to the frequency of exacerbations and proportion of SFDs using a log-linear model with a negative binomial distribution and an offset for each participant of time followed in the study.[41] Generalized linear models will compare the rate of exacerbations between ICS and placebo treatment arms within each phenotype group We will also explore interaction effects to see if phenotypes predict different treatment responses. Analyses will utilize a significance level of 0.05 without adjustment for multiple testing.

D. PITFALLS AND FUNDING. We anticipate that, similar to our preliminary findings in preschool-aged children, we will identify a phenotype distinguished by underlying Type 2 eosinophilic inflammation that will have differing exacerbation profiles, symptoms and responses to ICS. Our sample sizes should provide sufficient numbers to detect clinically meaningful results; our prior LCA of preschool children involved substantially fewer participants (N=1,708 for phenotype assessment, N=489 for outcome assessment) but still detected significant differences. We acknowledge that model selection can be subjective. LCA is a subset of structural equation modeling with foundations in the social sciences that is useful for identifying "class" (phenotype) membership among participants with multivariate categorical data. LCA was selected over clustering approaches because clustering methods: 1) divide data into groupings based on measures of "distance" between data points and are highly sensitive to outliers, 2) rely on interval or continuous data and there are potential concerns about variable scales and data assembly, and 3) have no objective criteria for judging the suitability of solutions.[42] LCA is model-based, permits differing variable measurement scales and variances, allows comparisons to be statistically tested, and is generally more appropriate for questionnaire-derived data.[43] Models of 1 to 10 latent classes will be repeatedly fitted with the number of latent classes in a stepwise fashion; model fit will be assessed as described above. It is also important to note that in our preliminary study of preschool children, exacerbations still occurred in each of the phenotype groups after ICS initiation. This observation suggests that some exacerbations may result from other triggers independent of Type-2 inflammation that are not suppressed by low-dose ICS. It is therefore our intent to leverage available biospecimens from these children in a future grant application (as delineated in Aim 3) to identify alternative endotypes and their associations with exacerbations. Ultimately, this project is in keeping with the mission of the NIH/NINR since asthma is a chronic disease with varying symptom and phenotypic expressions that may be amenable to personalized approaches. Our findings will therefore be used to support a future R01 application (PA-18-138, "Personalized Strategies to Manage Symptoms of Chronic Illness").

E. TIMELINE. This research will be completed in one year. The project is highly feasible given the time frame and could be launched immediately since it leverages previously collected data housed at the Pennsylvania State University (Dr. David Mauger, custodian). We anticipate at least two publications from this research and abstract presentations at national meetings.

HUMAN SUBJECTS RESEARCH

This research does not meet the definition of human subjects research as provided by the National Institutes of Health Office of Extramural Research. HHS regulations define "human subject" at 45 CFR 46.102 (f) as follows: "*Human subject*" means a living individual about whom an investigator conducting research obtains: 1) data through intervention or interaction with the individual, or 2) identifiable private information.

This research is limited to secondary analysis of coded, de-identified data and none of the investigators can ascertain the identity of participants.

OHRP does not consider research involving only coded information to involve human subjects as defined under 45 CFR 46.102(f) when:

1) The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals, and
2) The investigators cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain.

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