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Advances in Asthma 2016:**Designing Individualized Approaches to Management**

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Abbreviations

- AHR - airway hyperresponsiveness
- APIC - Asthma Phenotypes in the Inner City
- BAL - bronchoalveolar
- CAMP - Childhood Asthma Management Program
- CHW - community health workers
- COPD - chronic obstructive pulmonary disease
- DENND1B - differentially expressed in normal and neoplastic cells domain 1B
- DEP – diesel exhaust particle
- DMRT1 - Doublesex and mab-3 related transcription factor 1
- FDA - Food and Drug Administration
- FEF₂₅₋₇₅ - forced expiratory flow between 25% and 75% of the forced vital capacity
- FEV₁ - forced expiratory flow in one second
- HDM - house dust mite
- ICS - inhaled corticosteroid
- ILC2s - innate lymphoid cells
- LABA - long-acting beta-agonist
- miRNA - microRNA
- NAEPP - National Asthma Education and Prevention Program
- NIH – National Institutes of Health
- PCORI – Patient-Centered Outcomes Research Institute
- PEF - peak expiratory flow
- Post-AAI - post-allergic airway inflammation
- rAMs - resident alveolar macrophages

- 61 RSV – respiratory syncytial virus
62 RV – rhinovirus
63 SABA - short-acting beta-agonist
64 SLIT – sublingual immunotherapy
65 SNP - single nucleotide polymorphism
66 TET1 - Ten-eleven translocation 1
67 TLR – toll-like receptors
68 TRAP – traffic related air pollution
69 TSLP - thymic stromal lymphopoietin
70 WHO - World Health Organization
71 YKL-40 - chitinase 3-like protein-1

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77 **ABSTRACT**

78 In this years Advances in Asthma review we discuss viral infections in asthma and
79 potential therapeutic agents, the microbiome, novel genetic associations with asthma,
80 air quality and climate effects on asthma, exposures during development and long term
81 sequelae of childhood asthma, patient centered outcome research, and precision
82 medicine. In addition, we discuss application of biomarkers to precision medicine, and
83 new information on asthma medications. New evidence indicates that rhinovirus-
84 triggered asthma exacerbations become more severe as the degree of sensitization to
85 dust mite and mouse increase. The two biggest drivers of asthma severity were an
86 allergy pathway starting with allergic sensitization and an environmental tobacco smoke
87 pathway. In addition, allergic sensitization and blood eosinophils can be used to select
88 medications for management of early asthma in young children. These current findings,
89 among others covered in this review, represent significant steps towards addressing
90 rapidly advancing areas of knowledge that have implications for asthma management.

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95 sensitization, allergy, asthma, biomarkers, climate, COPD, eosinophils, exacerbation,
96 exhaled nitric oxide, genetics, ligelizumab, medication adherence, microbiome, patient-
97 centered outcomes, pregnancy, prenatal exposures, respiratory syncytial virus,
98 rhinovirus, rofumilast, tiotropium

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Introduction

Last year's Advances in Asthma focused on asthma across the lifespan and reported on some key observations related to asthma inception, the microbiome, and the epigenome. In addition, some aspects of predicting and preventing asthma exacerbations were featured (1). It is now clear that scientific advances are being made in many areas related to asthma, such as, epidemiology, immunology, microbiology, genetics, biomarkers, and new medications, so much so that it is a challenge for those writing asthma guidelines and strategies to synthesize this work and rapidly apply it to clinical practice. Therefore, reviews of key discoveries are important to keep the clinician abreast of these findings, so that they might be considered in the clinical setting while they await integration into asthma guidelines. This year, we discuss new findings reported in the Journal and other publications that relate to respiratory infections, air quality, factors that influence long-term outcomes, patient-centered outcomes research, precision medicine and new observations related to medications and asthma management.

Viral Infections in asthma and the promise of therapeutic targets

Respiratory viruses remain a key trigger of asthma exacerbations, providing insight into the evolution and pathophysiology of asthma. In a prospective observational cohort study involving 183 asthmatic children ages 6 to 17 years, Kantor et al (2) found that subjects with rhinovirus (RV) infection had more severe exacerbations than those participants with virus-negative exacerbations. In this cohort, RV-triggered asthma exacerbations became more severe as the degree of sensitization to dust mite and

mouse increased. Akin to the more severe exacerbations appreciated in the rhinovirus-infected children in the aforementioned study, Ducharme et al (3) performed a large, prospective, multicenter, cohort study in emergency departments revealing that viral detection was associated with failure of symptom management. Analyses from a large, prospective cohort of adults enrolled in an influenza surveillance study revealed that RV infection is prevalent in adults, with 11% of nasal/throat swabs testing positive for RV in adults presenting to the hospital, emergency department, or outpatient clinic with acute respiratory illness or fever (43).

In 2016, there was elucidation into the immune response induced by virus-triggered asthma exacerbations, identifying or further characterizing potential therapeutic targets. Han et al (5) illustrated the role of toll-like receptor (TLR) 2-expressing macrophages in the airway inflammatory response to RV, noting that TLR2+ macrophages were required for early stages of airway inflammation in their murine model. Additionally, transfer of wild-type macrophages to *Tlr2* knockout mice was sufficient to confer airway inflammation after RV infection. When IL-4-treated macrophages were similarly transferred, features akin to RV-infected mice with allergic airways disease were observed. Assessing the role of resident alveolar macrophages (rAMs) in respiratory syncytial virus (RSV) infection, Naessens et al (6) devised a post-allergic airway inflammation (post-AAI) murine model in which treatment with GM-CSF abrogated RSV-induced inflammation and airway hyperreactivity by means of maturing an apparent immature phenotype appreciated in the post-AAI rAM population. Through repeated inoculation of mice with low-dose virus and cockroach allergen, Lynch et al (7)

showed that co-exposure of respiratory virus and cockroach allergen induced a biphasic IL-33 response and impaired antiviral interferon production. Furthermore, IL-33 negatively regulated TLR7 signaling. Studying effects of RSV infection on group 2 innate lymphoid cells (ILC2s), another murine model showed proliferation and activation of IL-13-producing ILC2s via thymic stromal lymphopoietin (TSLP)-dependent mechanisms (8).

Characterization of the airway microbiome

Through detailed assessments of the airway microbiome, key differences between asthmatics, non-asthmatics, and those at risk for asthma have been characterized. Regarding at-risk populations, the nasopharyngeal microbiota of over one-thousand infants with bronchiolitis was analyzed as part of a large multicenter study (9). In this prospective cohort, infants with bronchiolitis due to RSV had a high abundance of *Firmicutes* and the genus *Streptococcus* and a low abundance of *Proteobacteria* and the genera *Haemophilus* and *Moraxella*, while infants with bronchiolitis due to RV had the opposite pattern. It is not clear if viral infections increase certain bacterial populations within a community and/or microbial community populations create environments suitable for viruses (9).

Addressing older individuals with established atopic phenotypes, a study orchestrated by AsthmaNet obtained bronchial brushings from 42 steroid-naïve, atopic asthmatic adults, 21 non-asthmatic but atopic adults, and 21 healthy control adults (10). By profiling samples via 16S rRNA gene sequencing, distinct differences in the bronchial bacterial microbiomes were appreciated in the 3 groups. Among asthmatic

adults, the bronchial microbiome at baseline differed according to their responsiveness to inhaled corticosteroid treatment. In a cross-sectional retrospective study assessing adult asthmatics that were not steroid-naïve, Denner et al (11) noted significant differences in the bronchial microbiome based on corticosteroid treatment. Further still, Sverrild et al (12) found that the level of eosinophilic airway inflammation correlates with variations in the microbiome across asthmatic patients.

Novel genetic associations with asthma and biologic impact of known gene variants

By discovery of new associations and demonstration of the biologic effects of known gene variations, the link between genetic changes and asthma expanded in 2016 (**Table 1**). Doublesex and mab-3 related transcription factor 1 (DMRT1) emerged as a novel candidate to potentially explain sex-specific asthma effects during childhood (13). A single nucleotide polymorphism (SNP) on chromosome 8 was associated with early lung function decline in two asthma cohorts, which was also associated with chronic obstructed pulmonary disease (COPD) (14). Exploring the mechanism by which SNPs at the differentially expressed in normal and neoplastic cells domain 1B (DENND1B) locus might lead to the development of asthma in young children, a *Dennd1b* knockout mouse model demonstrated the role of DENND1B in T cell receptor downmodulation in T_H2 cells (15). A new locus associated with time to asthma onset was identified at position 16q12 (16). Investigating the role of the previously reported 17q21 locus in asthma, a study by Schmiedel et al (17) detailed the deleterious effects exerted by asthma-risk variants on T cells. By analyzing the asthma-risk variant Glu-to-

Arg substitution at position 576 of human IL-4R α , new insights into the role of regulatory T cells and the development of T_H2-T_H17 inflammation were presented (18). Further assessing the known Gly-to-Arg substitution at the 16 position in the β 2-adrenoceptor gene, asthmatic children recruited from 5 cross-sectional studies identified the increased risk of asthma exacerbation with use of long-acting β -agonists in children carrying 1 or 2 alleles of the aforementioned substitution (19).

The influence of air quality and climate on asthma

Annesi-Maesano provided an overview of allergy specific health issues emerging due to climate change, as well as future directions regarding climate related health. Worldwide, only 12% of urban populations breath air that complies with World Health Organization (WHO) Air Quality Guidelines. Citing NASA data, we learn not only that the earth has experienced a 0.8°C/1.4°F average global temperature increase since the 1880s, but also that two-thirds of this warming has occurred since 1975. Components and consequences of this change: air pollution, floods, and plant life adaptation will impact population health, with the most vulnerable areas most effected, as well as our most vulnerable patients: the elderly, young, and poor (20). In the face of evolving climate challenges, new research has helped refine our understanding of how indoor and outdoor environments interact with the immune system and influence pulmonary physiology (**Table 2**).

Multiple letters to the editor in the fall of 2016 edition of *JACI* examined traffic related air pollution's (TRAP) influence on asthma. A median regression analysis of patients in a large birth cohort showed a significant association between increased

exposure to traffic-NO_x in the first year of life and increased adolescent airways resistance and reactance (21). Adolescent, self-reported psychosocial stress also seems to influence estimated pulmonary effects of TRAP. TRAP was associated with larger negative effects on lung function in households without a father present compared to homes with a father present. The authors speculate that hypothalamic axis modification secondary to stress might modulate immune function and enhance susceptibility to air pollution (22).

TRAP may also affect steroid sensitivity. In a mouse model of allergen-induced asthma with diesel exhaust particle (DEP) exposure, 4 days of dexamethasone treatment only partially reduced airway hyperresponsiveness (AHR) in mice exposed to both house dust mite (HDM) and DEP. These HDM + DEP exposed mice were noted to have greater airway neutrophilia compared to HDM only exposed mice. Anti-IL17A treatment in combination with dexamethasone significantly reduced AHR compared with either treatment alone (23).

Asthmatics suffer clinical symptoms quickly when exposed to worsening air quality. Explanations of the mechanism of this rapid sensitivity are now being reported. Many articles, as well as a recent review in *JACI* (24), have explained how innate lymphoid cells (ILCs) are emerging as key contributors to the pathogenesis of inflammatory disease. Group 2 ILCs produce type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13, upon stimulation with epithelium-derived cytokines, such as IL-33, IL-25, and TSLP.

A recent report by Yang et al revealed that BALB/c allergen-sensitized and allergen-challenged mice had elevated eosinophils in bronchoalveolar (BAL) fluid

following O₃ exposure (25). IL-5 release occurred within 12 hours after O₃ exposure, notably without increased T_H2 cells in the lung. Importantly, depletion of both ILCs and T cells, but not specific depletion of CD4⁺ T_H cells, abolished IL-5 release in BAL-fluid of O₃ exposed mice. These findings confirmed that ILC2s were the major source of IL-5 following O₃ exposure. The group went on to demonstrate a relationship between ILC2 and enhanced AHR in the setting of O₃ exposure (25). The timeline and pattern of inflammation in this study: type 2 cytokine release within hours leading to increased AHR following TRAP, helps describe how asthmatics may experience symptoms quickly and have heightened sensitivity to air pollution.

Previous work has shown that TRAP is associated with DNA methylation variation. Ten-eleven translocation 1 (*TET1*) enzyme is a promoter of DNA demethylation. Cross sectional data from non-twin siblings discordant for asthma, born and raised in the same household, showed an association between asthma status and demethylation of a CpG site in the promoter region of the *TET1* gene. In addition, this study showed that methylation of the same CpG site was associated with TRAP exposure (26). The exact role of *TET1* in influencing these associations remains unknown, and the authors suggest *TET1* warrants further study as a possible systemic biomarker for childhood asthma.

In addition to air pollution's effects, data continues to emerge on specific microbial exposures that may influence asthma development. Fungal and bacterial community characteristics were measured in the main living area of asthmatic children using next-generation DNA sequencing technology. Participants were selected at the extremes of asthma severity. Amongst all children, increased asthma severity was

associated with high concentrations of allergenic species, high total fungal concentration, and increased bacterial richness. In addition, fungal and bacterial community composition shared more similarities in homes of severe asthmatics compared to mild asthma. While no specific bacterial operational taxonomic units were significantly associated with asthma severity, the fungal genus *Volutella* was found to be associated with asthma severity (27).

Prior work has shown that children raised on traditional dairy farms demonstrate protection from asthma and allergic disease. Stein et al recently looked at environmental exposures, genetic ancestry, and immune profiles in both Amish and Hutterite U.S. populations (28). These two groups live similar lifestyles with the notable exception that the Hutterites utilize more industrialized farming practices. Genome wide SNPs compared allele frequencies and showed strong similarities between the groups, indicating similar genetic ancestry. Markers of atopy were lower in the Amish group than the Hutterite group. After 1 month of sampling from electrostatic dust collectors in 10 homes from both groups, Amish homes had endotoxin 6.8 times higher than Hutterite homes. Amish children had increased proportions of neutrophils, lower proportions of eosinophils, and monocytes with a more suppressive phenotype than Hutterite children. The Amish also had genetic overexpression of components of the innate immune response to microbial stimuli. An ovalbumin mouse model of allergic asthma, following administration of Amish house dust intranasally, demonstrated inhibited AHR, BAL eosinophilia, and ovalbumin specific IgE (28). For additional information on the microbiome's influence on early asthma development, readers are directed to the recent review by Erika von Mutius (29).

Exposures during different stages of development and long term sequelae of childhood asthma

Amongst the well described risk factors for asthma, recent research is helping to define the level of influence these risk factors have. The Inner City Asthma Consortium conducted a causal network analysis on a conceptual model of 8 potential asthma risk-factor domains. They found that the model could explain about 50% of the variance in asthma severity. The two biggest drivers of asthma severity were an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway. Among the individual domains, pulmonary physiology and rhinitis severity had the largest effects on asthma severity (30). Analysis of an Australian longitudinal birth cohort demonstrated that allergic sensitization by 12 months of age was associated with increased risk of wheeze during young adulthood, as well as lower FEV₁, FEV₁/FVC ratio, and FEF₂₅₋₇₅ at 24 years of age (31). The contribution of allergic sensitization and respiratory pathogens (viral, as well as bacterial) was reviewed last year by Jackson and colleagues for the clinical reviews series in *JACI* (32).

In a pregnancy cohort, the relative importance of prenatal and postnatal stress on asthma was assessed. After adjusting for confounders, a dose-response relationship emerged with an increase in the odds of asthma diagnosis for each increase in maternal stress category both prenatally and postnatally (33). A meta-analysis found that compared with term-born children, premature children had a lower FEV₁, FEV₁/FVC ratio, and FEF₇₅ at a mean age of 8.5 years. Similar findings were seen in children born with low birth weight. Mediation analyses suggested that FEV₁, FEV₁/FVC, and FEF₇₅

might explain 7-45% of the associations between early growth characteristics and asthma. These associations were present across the full range of early growth, an observation with possible population health implications (34).

In addition to defining early influencers of airflow obstruction, we are learning more about the long term effects of airflow obstruction. A latent class analysis of over 12,000 participants followed from infancy into adolescence identified 6 different wheezing phenotypes. Phenotypes characterized by remitting symptoms in later childhood still were associated with lung function deficits in adolescence compared to the never/infrequent wheezing phenotype. All 3 phenotypes with persistent symptoms had strong associations with diagnosed asthma, bronchodilator reversibility, and high exhaled nitric oxide values in adolescence. Late onset wheezing was not associated with airway obstruction by 15 years. The associations suggest wheezing illnesses with onset early in life have a greater influence on lung function than wheezing duration (35). McGeachie and colleagues highlighted long term deficiencies in lung function in Childhood Asthma Management Program (CAMP) participants followed into the third decade of life. Despite this cohort comprising mild to moderate asthmatics, investigators found that a high proportion (75%) of subjects had reduced lung function as adults. Notably, 11% of participants met spirometric criteria for COPD (36).

Patient-centered outcomes research reflects patient priorities and engages stakeholders

The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (37), last updated in 2007, provides guidance for the management of asthma. It

is informed for the most part by efficacy studies. These narrowly defined studies include patients most likely to benefit and who are treated under the most promising conditions. However, a limitation of these well-controlled studies is that the interventions are not always effective when applied in the real-world, do not take into account the uniqueness of patients and their environments, and often exclude those with comorbidities. This limitation is particularly evident when applying recommendations to patients from low income and minority communities where resources are limited and social barriers to accessing healthcare and carrying out management recommendations are common (38).

Additionally, interventions prompting guideline recommendations may not reflect individual patient priorities, for example a patient's concern about taking many medications for a variety of conditions or their cost. Thus, patient-centered studies are needed to address health disparities. The December issue of the Journal is devoted to patient-centered comparative effectiveness research focusing on research funded by the Patient-Centered Outcomes Research Institute (PCORI). PCORI's mission is to fund comparative effectiveness research that allows patients and other stakeholders of research to make informed health decision (39).

In presenting the PCORI perspective, Anise and Hasnain-Wynia argue for the importance of engaging these stakeholders, which include patients and healthcare providers, in all aspects of the research, that is, the development of the intervention design, selection of outcome measures, refinement and conduct of the research, analysis, and reporting of the results (40). Bryant-Stephens and colleagues describe the experiences of community health workers (CHWs) as they make home visits to

asthmatic adults in low-income urban neighborhoods, many living in one-room apartments or overcrowded spaces with many family members (41). Martin and colleagues report the challenges of overcoming barriers in transitioning care for children with asthma from the emergency department to stable consistent outpatient care (42). An analysis of the methodologies of 8 PCORI-funded studies concludes with recommendations for modifying traditional research methodology to overcome obstacles in patient-centered intervention research. Modifications may include devoting more resources than in a traditional study for recruitment and conduct of the study in order to maintain enrollment and to minimize but account for missing data (43).

Clinical Risk Factors

Wells and colleagues (44) add support to this patient-centered approach by demonstrating that neither self-reported race-ethnicity nor race defined by genetic ancestry predicted ICS response; rather baseline lung function and self-reported asthma control do, emphasizing the need to find ways to ensure optimal lung function, asthma control, and elimination of barriers to accessing care. Szentpetery and colleagues (45) describe asthma risk factors among Puerto Ricans, including exposure to environmental tobacco, violence, pollution, and psychological stress along with personal risk factors such as obesity, difficult access to health care, and low health literacy. The authors conclude multifactorial interventions are needed (45).

Liu et al (30) in the longitudinal Asthma Phenotypes in the Inner City (APIC) Study analyzed pathways through which risk factors contribute to asthma severity in inner city children, suggesting multi-factorial interventions such as exposure to

environmental tobacco smoke and to allergens, will address asthma severity (**Table 3**). Their model explained 53.4% of the variance in asthma severity of the cohort of 561 children. The authors illustrated their points using a new Journal feature, a graphical abstract. In another APIC analysis, Zoratti et al (46) used cluster analysis to define phenotypes of inner city children with asthma, including one phenotype of severe asthmatic children that were highly allergic. Also from the APIC Study, Pongracic et al (47) examined children and adolescents with difficult to control asthma, defined as requiring high dose inhaled corticosteroids, and found them distinguishable from those requiring only low dose inhaled corticosteroids by FEV₁ bronchodilator responsiveness, rhinitis severity, and atopy. Other studies found exacerbations vary by season in inner-city asthma children [48] and in youth living in poverty whether urban or rural [49, 50]. The pathways and heterogeneity of risk factors emphasize that in multifactorial intervention studies informed by these analyses, addressing poverty and engaging the children and their caretakers in interventions is essential.

In considering patient engagement in healthcare, navigating skill, the ability to access healthcare and communicate with providers, is an important skill. Perez et al (51) developed and validated a questionnaire with input from patients to assess navigation. More important than the development of the questionnaire, they found an item of the questionnaire, also routinely a part of a patient-provider interview (for example: Tell me the names of your asthma medications) was correlated with more general health literacy. Thus, a routine interview question yields much information about the patient.

Precision Medicine

In January 2015 President Obama proposed a Precision Medicine Initiative (52) considering each patient's uniqueness and the need for tailoring treatment to take into account individual variability in genes, environment, and lifestyle. This initiative aligns with translational and comparative effectiveness research seeking to understand environmental, clinical, and lifestyle risk factors that characterize phenotypes and identifying the biomarkers to help define the pathophysiologic mechanisms or endotypes in order to tailor preventive and ongoing medical care for each individual (53 - 55).

Berry and Busse review currently used biomarkers (56). Muraro and coauthors collaborated under PRACTALL, an initiative of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology, to harmonize approaches and to summarize endotypes and validation of biomarkers in order to develop precision medicine for management of asthma and other atopic diseases (57). With this focus on biomarkers, how exposure to the environment including the microbiome, and also how the phenotype of poverty (41) result in relevant biomarkers needs to be understood. Thus, the contributions of real-world and comparative effectiveness research with participation from stakeholders are essential to complete the translation of research from bench to bedside (53).

Application of biomarkers to personalized medicine

In 2012, the Journal published a report from the NIH Asthma Outcomes Task force to summarize relevant outcomes for NIH asthma research. One of the sections

was on physiology and listed various physiologic measures as core (should be included in all asthma research), supplementary (applied in selected research), and exploratory (intended to be evaluated for potential application) (58). AHR by methacholine challenge was listed as a supplemental measure. Pralong et al (59) reported on the predictive value of nonspecific airway responsiveness in bronchial asthma. Based on data from a Canadian database of 1,012 cases, they indicated that a negative methacholine challenge in a patient still exposed to the causative agent at work makes the diagnosis of occupational asthma unlikely.

The Outcomes Report stated that FEF_{25-75} is not a specific measure of small airway obstruction, but could be chosen as an endpoint, however its value is less established (58). Siroux et al (60) studied 337 participants with 142 children and 225 adults for persistence of current asthma and risk for uncontrolled asthma and concluded that decreased FEF_{25-75} , as an indicator of small airway obstruction, might contribute to long-term persistence of asthma and subsequent risk for poor asthma outcomes independently from effects of the large airways.

Another section of the NIH Outcomes Task Force addressed biomarkers (56). Berry and Busse (56) provided an updated review on biomarkers in asthma and indicated that certain biomarkers, such as sputum and blood eosinophils, can help define the specific pathophysiology of different asthma phenotypes and identify potential therapeutic agents. Similarly, Muraro et al (57) indicated that progress has been made in profiling the type 2 immune-response driven asthma, but the endotype driven approach for non-T2 immune response for asthma is lagging behind. It will be important to define validated and qualified biomarkers for research and for precision medicine.

Skevaki et al (61) indicated that biomarker discovery and validation in children with disease lag behind those in adults; given the early onset and potential lifelong effect of the disease. The ultimate challenge will be optimization of prevention strategies that can be implemented in children identified as being at risk of a noncommunicable disease, such as asthma, through the use of biomarkers.

Blood and sputum eosinophils, along with exhaled nitric oxide were listed as supplementary biomarkers to be considered optional in asthma research (62) (**Table 4**). Zeiger et al (63) reported observations from a Kaiser-Permanente Southern California database of patients 12 years and older, that a high blood eosinophil count (≥ 400 cells/mm³) was an independent risk factor for 2 or more asthma exacerbations or any asthma emergency department visit or hospitalization, but not direct costs in patients with severe uncontrolled asthma.

A study conducted in the NHLBI AsthmaNet reported that in young children with asthma necessitating Step 2 treatment, phenotyping with allergen sensitization, considered a core biomarker in the Asthma Outcomes Report, and a blood eosinophil count of 300 cells/mm³ or greater, is a useful guide for treatment selection and identifies children with a high exacerbation probability for whom treatment with a daily inhaled corticosteroid is beneficial despite risks of growth suppression (64).

A Paradigms and Perspectives review (65) summarized key lessons learned for the application of exhaled nitric oxide in clinical practice. Exhaled nitric oxide measurement can be an important tool in the management of asthma and there is a need for asthma guidelines to define its application, so that it can be more readily applied in the primary care setting, where the majority of asthma patients are managed.

Additional reports demonstrated that a combined high exhaled nitric oxide level and blood eosinophils related to a higher likelihood of AHR and uncontrolled asthma in young asthmatic patients (66).

Michils et al (67) measured exhaled nitric oxide in relation to β 2-agonist use and identified three exhaled nitric oxide behaviors to identify the site of airway obstruction in asthmatic patients. A note of precaution was provided by Cohen et al (68) indicating that exhaled nitric oxide levels were not associated with an asthma diagnosis, wheezing symptoms, lung function measures, or prior morbidity in children with sickle cell anemia but were associated with markers of atopy and increased risk of future acute chest syndrome.

Periostin was a newly reported biomarker at the time of the NIH Asthma Outcomes Report and thus was not fully addressed in that report and would have been considered exploratory at the time. Periostin is considered an extracellular matrix protein that is upregulated by type 2 cytokines interleukin-4 and 13 in bronchial epithelial cells and lung fibroblasts (69). Johansson et al (69) demonstrated that serum periostin is not associated with asthma severity, but is associated with type 2 immunity in patients who are symptomatic despite their use of corticosteroids and potential use for assessing greater response to type-2 immunity based treatment. Noguchi et al (70) reported that periostin upregulates eosinophil functions such as superoxide anion generation and eosinophil-derived neurotoxin release, along with the production of TGF- β and cysteinyl leukotrienes from eosinophils.

As further studies are being conducted, new biomarkers are being discovered. Hinks et al (71) reported on 6 clinicopathobiologic clusters based on blood and induced

sputum measures. They implied from their studies that IL-5 production is relatively steroid insensitive and the expression of chitinase 3-like protein-1 (YKL-40) is present in patients with neutrophilic inflammation along with the expression of metalloproteinases in patients with severe asthma.

There is increasing interest in the use of specific microRNA (miRNA) expression profiles with inflammatory cell profile and diseases severity in asthmatic patients. Maes et al (72) reported that expression of miR-223-3p, miR-142-3P, and miR-629-3p is increased in sputum of patients with severe asthma and is linked to neutrophilic airway inflammation, perhaps a new way to identify this asthma inflammatory phenotype. Panganiban et al (738) demonstrated that circulating miRNAs are uniquely expressed in patients with allergic rhinitis and asthma and have the potential for use as noninvasive biomarkers to diagnose and characterize these diseases. Expression of miRNAs and genes associated with bronchial immune responses were demonstrated to be significantly modulated by diesel exhaust or allergens and thus might be used as biomarkers of exposure to air pollution as an indicator of epithelial wall damage (74).

There is also great interest in identifying biomarkers that may be reflective of asthma development in utero. Magnus et al (750) reported that high maternal levels of neopterin, a marker of cellular immune activation, during pregnancy were positively associated with asthma in offspring, but further studies are needed to identify the mechanism for this observation. There is also interest in using breathomics with the assessment of volatile organic compounds in assessment of asthma and COPD. Large multicenter studies will be needed to validate this noninvasive technology before clinical

applications can be made for chronic airways disease assessment, phenotyping and monitoring (76).

Another biomarker considered exploratory by the Biomarkers Committee (56) was airway imaging. This field continues to move along and holds promise for new ways to assess airway disease. Gonem et al (772) used hyperpolarized ^3He diffusion magnetic resonance to determine the nature of acinar airway involvement in asthmatic patients. They demonstrated alterations in long-range diffusion within the acinar airways and gas trapping but the precise anatomic nature and mechanistic role in patients with severe asthma requires further evaluation. Hartley et al (78), using thoracic quantitative computed tomography, reported that in asthmatic patients and patients with COPD, lung function impairment is strongly associated with air trapping, with a contribution from proximal airway narrowing in asthmatic patients.

Therefore, since the 2012 report on biomarkers for the NIH Asthma Outcomes Task Force, information regarding certain biomarkers has been refined, new biomarkers discovered, and information is being rapidly accumulated on the exploratory category of biomarkers to refine their application.

New information on asthma medications

In 2016, promising new medications as add-on management for poorly controlled asthma were introduced, and the safety of well-established medications, namely LABAs, was revisited. The addition of roflumilast, a selective phosphodiesterase 4 inhibitor, in conjunction with montelukast to the controller regimen of adult patients with inadequately controlled asthma despite the use of at least medium-dose ICSs with a LABA resulted in a statistically significant increase in pre-bronchodilator FEV₁ from

baseline, improved morning PEF, and improved daytime symptom scores compared to placebo with montelukast (79). However, there was no change in pre-bronchodilator PEF or asthma control questionnaire scores (79).

QGE031 (ligelizumab), an anti-IgE antibody with a higher binding affinity for IgE than omalizumab, elicited a 3-fold and 16-fold greater increase in provocative allergen concentrations to decrease the FEV₁ by 15% compared to omalizumab and placebo, respectively, in adult patients with mild allergic asthma (80). QGE031 also elicited a suppression of allergen-induced skin prick test responses that was greater than that of placebo or omalizumab (80).

Once-daily tiotropium delivered via the Respimat Soft Mist inhaler (Boehringer Ingelheim; Ingelheim am Rhein, Germany) in addition to background ICS therapy, with or without a leukotriene receptor antagonist, improved the peak and trough FEV₁, FEF₂₅₋₇₅, and pre-dose morning and evening PEF in adolescent patients (81).

In adults with not well controlled house dust mite (HDM) allergy-related asthma, HDM sublingual immunotherapy (SLIT) improved the time to the first moderate or severe asthma exacerbation, primarily due to an effect on moderate asthma exacerbations, compared to placebo during an ICS reduction phase (82). HDM SLIT did not change asthma control questionnaire or asthma-related quality of life scores compared to placebo (82).

The benefit of the aforementioned add-on medications primarily center on their ability to improve lung function (79-81). Additional studies to examine their impact on asthma control, including risk and impairment, would be beneficial as they are explored as novel controller therapies.

The United States Food and Drug Administration (FDA) issued a public health advisory on the safety of LABA-containing products in 2005 in response to the Salmeterol Multicenter Asthma Research Trial findings (78). Following this activity, there was statistically significant decrease in fixed-dose ICS-LABA use in children and adults, with a concurrent increase in ICS and leukotriene modifier use, based on prescription database analysis (83).

Subsequently, the FDA mandated post-marketing safety studies examining the effect of ICS-LABA combination therapy on serious asthma-related events, including death, intubation, and hospitalization (84-86). In adolescents and adults, fixed-dose budesonide-formoterol and fluticasone-salmeterol combination therapies were non-inferior to budesonide or fluticasone alone, respectively, for serious-asthma related events (84, 85). Similarly, in pediatric patients, fluticasone-salmeterol was non-inferior to fluticasone alone for serious asthma-related events (86). The risk of a severe asthma exacerbation was significantly lower in adult and adolescent patients treated with combination ICS-LABA therapy compared to ICS therapy alone (84,85), but this medication effect was not observed in pediatric patients (86). The impact of these studies on the FDA's overall assessment of fixed-dose ICS-LABA controller therapy safety remains to be seen.

Management

In 2016, emphasis was placed upon the assessment of medication adherence and the creation of comprehensive school-based asthma support networks (**Table 5**). In a population-based cohort study, only 33% of pediatric patients demonstrated high ICS

adherence (87). Similarly, using reimbursement data, only 24% of adults and pediatric patients maintained regular ICS adherence one year after a period of regular ICS use (88). The unique barriers for poor medication adherence are age-specific requiring tailored approaches (89). In addition, inhaled medications pose a unique challenge to adherence, requiring proper technique for adequate drug delivery (90).

Technological advances are exploring ways to address poor adherence. Use of the Propeller Health Asthma Platform (Propeller Health; Madison, WI), an electronic monitoring device system, decreased SABA use and increased SABA-free days in children and adults (91). Utilization of an acoustic recording device attached to an inhaler found that only 20% of patients used their inhaler in the correct manner at the correct interval, emphasizing the need to address not only number of actuations but also technique errors (92).

The School-based Asthma Management Program (SAMPRO) was developed to foster multidirectional communication between children, families, clinicians, school-based personnel, and the community to promote better pediatric asthma care (88). SAMPRO identified four essential components to create this partnership: a circle of support between the aforementioned groups, asthma management plans, comprehensive asthma education for school personnel, and assessment and remediation of school-based asthma triggers (93).

The benefit of such a multidisciplinary, school-based program was highlighted through the Step-Up Asthma Program, which utilized asthma counselors as a bridge between subspecialty asthma care, primary care providers, school nurses, and families (94). Over a 2-year period, the program increased the number of asthma action plans,

increased rescue and controller medications in schools, improved asthma knowledge scores, improved inhaler technique, and reduced asthma exacerbations (89).

Summary

As indicated in this summary, there are rapid areas of development related to the natural history of asthma and the impact of the environment (**Table 6**). There has been no previous era in asthma management that has witnessed the introduction of so many new classes of medications. It will be a challenge for clinicians and those contributing to asthma guidelines to select relevant pieces of information that should be incorporated into clinical practice. Meanwhile, clinicians must keep up with these new findings in order to provide benefits to patients by implementing strategies that are most likely to be effective. We will continue to monitor this literature and highlight those key findings that have the potential to alter asthma management and report on them in our annual review.

Table 1: Summary of novel genetic associations with asthma and biologic impact

- Doublesex and mab-3 related transcription factor 1 (DMRT1) potentially explains sex-specific asthma effects during childhood (13).
- A single nucleotide polymorphism (SNP) on chromosome 8 was associated with early lung function decline and chronic obstructed pulmonary disease (COPD) (14).
- A new locus associated with time to asthma onset is at position 16q12 (16).
- Gly-to-Arg substitution at the 16 position in the β 2-adrenoceptor gene in asthmatic children was associated with an increased risk of asthma exacerbation with use of long-acting β -agonists in children carrying 1 or 2 alleles of this substitution (19).

Table 2: New findings related to studies on air quality, pollution, climate, environment and asthma

- Patients in a large birth cohort showed a significant association between increased exposure to traffic-NO_x in the first year of life and increased adolescent airways resistance and reactance (21).
- A mouse model of allergen-induced asthma with diesel exhaust particle (DEP) exposure, demonstrated that 4 days of dexamethasone treatment only partially reduced airway hyperresponsiveness (AHR) in mice exposed to both house dust mite (HDM) and DEP (23).
- A causal network analysis on an inner city asthma cohort demonstrated that the two biggest drivers of asthma severity appears to be an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway (30).
- Analysis of an Australian longitudinal birth cohort demonstrated that allergic sensitization by 12 months of age was associated with increased risk of wheeze during young adulthood, as well as lower FEV₁, FEV₁/FVC ratio, and FEF₂₅₋₇₅ at 24 years of age (31).
- After adjusting for confounders in a pregnancy cohort, a dose-response relationship emerged with an increase in the odds of asthma diagnosis in children for each increase in maternal stress category both prenatally and postnatally (33).

Table 3: Analyzing predictors of severe asthma from NIAID Inner City Asthma Consortium

- Multi-factorial interventions, such as exposure to environmental tobacco smoke and to allergens, must be used to address asthma severity (30).
- A cluster analysis methodology was used to define phenotypes of inner city children with asthma, including one phenotype of severe asthmatic children that is highly allergic (46).
- Children and adolescents with difficult to control asthma, defined as requiring high dose inhaled corticosteroids, are distinguishable from those requiring only low dose inhaled corticosteroids by FEV₁ bronchodilator responsiveness, rhinitis severity, and atopy (47).

Table 4: Useful biomarkers for personalized medicine for asthma

- In patients with severe uncontrolled asthma, 12 years and older, a high blood eosinophil count (≥ 400 cells/mm³) was an independent risk factor for 2 or more asthma exacerbations or any asthma emergency department visit or hospitalization, but not direct costs (63).
- In young children with asthma necessitating Step 2 treatment, phenotyping with allergen sensitization and a blood eosinophil count of 300 cells/mm³ or greater, identifies children with a high exacerbation probability for whom treatment with a daily inhaled corticosteroid is beneficial despite risks of growth suppression (64).
- A combined high exhaled nitric oxide level and blood eosinophils related to a higher likelihood of airway hyperresponsiveness and uncontrolled asthma in young asthmatic patients (66).
- Serum periostin is not associated with asthma severity, but is associated with type 2 immunity in patients who are symptomatic despite their use of corticosteroids and potential use for assessing greater response to type-2 immunity based treatment (69).
- Expression of microRNAs and genes associated with bronchial immune responses were demonstrated to be significantly modulated by diesel exhaust or allergens and thus might be used as biomarkers of exposure to air pollution as an indicator of epithelial wall damage (74).

Table 5: New insights relevant to asthma management

- Using reimbursement data, only 24% of adults and pediatric patients maintained regular ICS adherence one year after a period of regular ICS use (88).
- Use of an electronic monitoring device system, decreased SABA use and increased SABA-free days in children and adults (91).
- The mission of the Patient-Centered Outcomes Research Institute (PCORI) is to fund comparative effectiveness research that allows patients and other stakeholders of research to make informed health decision (39).
- The School-based Asthma Management Program (SAMPRO) was developed to foster multidirectional communication between children, families, clinicians, school-based personnel, and the community to promote better pediatric asthma care (88).
- A multidisciplinary, school-based program can increase the number of asthma action plans, increase rescue and controller medications in schools, improve asthma knowledge scores, improve inhaler technique, and reduce asthma exacerbations (89).

Table 6. Key advances in 2016

- Rhinovirus-triggered asthma exacerbations become more severe as the degree of sensitization to dust mite and mouse increased (2).
- Co-exposure of respiratory virus and cockroach allergen induced a biphasic IL-33 response and impaired antiviral interferon production (7).
- Infants with bronchiolitis due to RSV had a high abundance of *Firmicutes* and the genus *Streptococcus* and a low abundance of *Proteobacteria* and the genera *Haemophilus* and *Moraxella*, while infants with bronchiolitis due to rhinovirus had the opposite pattern (9).
- Cross sectional data from non-twin siblings discordant for asthma, born and raised in the same household, showed an association between asthma status and demethylation of a CpG site in the promoter region of the *TET1* gene (26).
- The two biggest drivers of asthma severity were an allergy pathway starting with allergic sensitization and an environmental tobacco smoke pathway (30).
- Wheezing illnesses with onset early in life have a greater influence on lung function than wheezing duration (35).
- Precision Medicine and patient-centered research including the contributions of stakeholders are needed (40).
- Ability to list asthma medications is associated with higher levels of health literacy (51).
- Biomarkers including exhaled nitric oxide and eosinophil counts have potential as indicators of endotypes (56).

- Allergen sensitization and blood eosinophils can be used to select medications for management of asthma in young children (64).
- In a population-based cohort study, only 33% of pediatric patients demonstrated high ICS adherence (87).
- Utilization of an acoustic recording device attached to an inhaler found that only 20% of patients used their inhaler in the correct manner at the correct interval, emphasizing the need to address not only number of actuations but also technique errors (92).

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