Advances in adult asthma diagnosis and treatment and health outcomes, education, delivery, and quality in 2011: What goes around comes around

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Last year's review of research advances in adults with asthma emphasized the linear trajectory of translation: the initial studies translating bench findings to the first patients (T1) are connected to larger efficacy studies, including clinical trials studying subjects under tightly controlled conditions (T2), and these in turn are connected to research, including comparative effectiveness research, that tests how the efficacy findings of T2 research fare in the real world, diverse populations, and varied practice settings (T3). This year what was observed was a more interwoven relationship (rather than a linear one), in which each translational level informs the others and new approaches to answering old questions have led to new discoveries. Within this framework, the present review summarizes clinical research on asthma in adults that was reported in the *Journal of Allergy and Clinical Immunology* in 2011, with emphasis on health outcomes, education, delivery, and quality in terms of discoveries related to mechanisms of disease, environmental exposures, and management. (J Allergy Clin Immunol 2012;129:69-75.)

Key words: *Asthma, adults, genetics, genome-wide association study, inhaled corticosteroids, biomarkers, long-acting β-agonist, tiotropium*

Abbreviations used

ED:	Emergency department
GWAS:	Genome-wide association study
HAPN:	High-asthma-prevalence neighborhood
HEDQ:	Health outcomes, education, delivery, and quality
ICS:	Inhaled corticosteroid
JACI:	*Journal of Allergy and Clinical Immunology*
LAPN:	Low-asthma-prevalence neighborhood
MEPS:	Medical Expenditure Panel Survey
NHIS:	National Health Interview Survey
NHLBI:	National Heart, Lung, and Blood Institute
SES:	Socioeconomic status
SLIT:	Sublingual immunotherapy
SNP:	Single nucleotide polymorphism

Like past Advances reviews pertaining to asthma relevant to adults,[1,2] this year's summary of research reported in the *Journal of Allergy and Clinical Immunology* (JACI) focuses on pathophysiology and genetics, the role of environmental exposures, the relationship of obesity to asthma, and approaches to asthma management. One dominant theme that emerges is the quest for new answers to old questions. For example, Szefler[3] asks whether it is time to revise the guidelines for asthma diagnosis and management. Although there are fewer new therapeutics, there is new information on the roles of tiotropium and omalizumab. Questions about when to "step up," "step down," or "step off" therapy remain, as does controversy regarding the safety and efficacy of long-acting β-agonists.[4] The old argument about the importance of inflammatory response versus other mechanisms is again under study in asthma pathogenesis.[5-7] In their quest to better answer these and other lingering questions, researchers frequently use clinical information to inform their hypotheses. For example, Fitzpatrick et al[8] used a cluster analysis of clinical traits to reclassify children with severe asthma, allowing them to generate new hypotheses to study asthma's mechanisms. Other researchers examined study subjects according to their "endotypes" or functional or pathophysiologic mechanisms, such as "aspirin sensitive" or "allergic bronchopulmonary mycosis," rather than by conventional clinical characteristics or "phenotypes."[9] This review summarizes research reported in the JACI in 2011, addressing these and other questions, along with some key references from other journals framed in terms of an interwoven T1-T2-T3 paradigm, progressing from mechanisms of disease to the effect of the environment and then reviewing advances in asthma management in adults.

MECHANISMS OF DISEASE

Physiology

There is renewed interest in airway remodeling focusing on non-T_H2 mechanisms and innate immunity in asthma pathophysiology,[7,10] stemming in part from the observation that not all patients with asthma are steroid responsive. Xiao et al[11] found patchy disruption of tight junction complexes in cultures of bronchial epithelium from asthmatic patients that was not observed in healthy control subjects. Exposing the cultures to cigarette smoke extract worsened the disruption, whereas incubation with epidermal growth factor induced tight junction formation and prevented disruption, suggesting that loss of lower airway epithelial integrity contributes to asthma pathogenesis. Grainge et al[12] found that compressive mechanical forces induced by methacholine produced airway remodeling independent of allergen-induced T_H2-dependent inflammation in atopic adults. Wood et al[13] presented

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data suggesting that diet, particularly high-fat meals, can augment neutrophilic airway inflammation and suppress bronchodilator recovery, also implicating the innate immune system. Chang et al[14] found T_H17 cytokines induced human airway smooth muscle cell migration and thus may play a possible role in the airway remodeling in asthma independent of T_H2.

Andersson et al[15] found greater numbers of both tryptase-positive and tryptase-chymase-positive mast cells, both populations with increased expression of FcεRI, in the alveolar parenchyma of atopic patients with asthma uncontrolled by inhaled corticosteroids (ICSs) in comparison with control subjects who were either nonatopic or had only allergic rhinitis.

Variations in the microbial colonization of the epithelial environmental borders of the gut[16] and respiratory tract[17] are being analyzed for their possible role in asthma pathogenesis. A National Heart, Lung, and Blood Institute (NHLBI) Asthma Clinical Research Network study by Huang et al[17] compared the airway microbiota and bronchial hyperresponsiveness of 65 adults with suboptimally controlled asthma with those of healthy control subjects. The investigators reported higher bacterial burden and diversity in the asthmatic cohort and found that the presence of certain species, including Comamonadaceae, Sphingomonadaceae, and Oxalobacteraceae, correlated with bronchial hyperresponsiveness to methacholine.

Studies are also underway to determine whether exposure to the maternal microbiome during vaginal delivery compared with cesarean section delivery or home birth versus hospital birth differentially influences the development of atopic disease in the infant.[16] In such research it is difficult to control for unidentified confounders, such as that infants born at home might be more likely to have healthy parents and a healthy gestation.

Genetics

More than 200 genes have been associated with asthma in candidate-gene and genome-wide association studies (GWASs), but most of these findings have not been replicated.[10,18] GWASs are as good as the genetic and clinical data used,[19,20] and identified genes generally account for only a tiny portion of the heritability of a complex disease. In addition, the identified gene might, through linkage disequilibrium, be associated with a relevant but ungenotyped gene.[21]

Most study subjects have been of European descent.[22] Mexicans and Puerto Ricans have been classified collectively as "Hispanics/Latinos," but the 2 populations have different asthma prevalence, severity, and mortality. Galanter et al[22] sought to compare in these 2 groups the occurrence of genes previously associated with asthma in either at least 2 candidate-gene studies or a GWAS. They tested these associations in 2 Latino populations: (1) Puerto Rican probands recruited from Puerto Rico and New York City and (2) Mexican probands recruited from Mexico City and the San Francisco Bay area. Genotyping was performed on a gene chip array, and an additional single nucleotide polymorphism (SNP)–based replication procedure was used. Of 124 genes previously identified, 17 genes with 32 SNPs were associated with asthma in at least 1 of the populations. Twenty-two of these SNPs in 11 genes were in the combined population; 5 SNPs were associated in only 1 population. In a gene-based approach 2 additional genes were associated with asthma in the combined population, and 3 additional genes were associated with asthma in only one. SNPs from ORM1-like protein 3 *(ORMDL3)*, *GSDMB*, and *IL33* replicated in both populations. Thus only a small number of previous genetic association studies replicated in the combined population of Mexican and Puerto Rican asthmatic subjects. Although most of the SNPS were identified in both groups, there were several population-specific associations. These findings suggest that risk factors for asthma include environmental and social exposures in addition to genetics and that the genetic makeup of Hispanic/Latino groups needs further study.

Loisel et al[23] searched for a genetic explanation of sex differences in asthma; they examined *IFNG*. The investigators had previously demonstrated that sex modified the association between IFN-γ production and wheezing phenotypes in children with a parental history of atopy. In this 2011 study using data from the Childhood Origins of Asthma birth cohort, the investigators found that sex modified the association between *IFNG* polymorphisms and wheezing illnesses in the first 3 years of life. Heterozygosity of 2 *IFNG* SNPs was protective in girls but was associated with increased risk of asthma in boys.

In a nested case-control genetic association study of children of white European ancestry from the Isle of Wight birth cohort, a previously unreported association with asthma susceptibility was found in and around the ATP synthase mitochondrial F1 complex assembly factor 1 gene *(ATPAF1)*.[24] Also in 2011, a GWAS identified an association of the IL-6 receptor gene on 1q21 with patients from Australia with a physician's diagnosis of asthma; the authors speculate that toclizumab, an IL-6 receptor antagonist with efficacy in rheumatoid arthritis, might also be therapeutic in asthmatic patients.[25] The same authors also identified an SNP belonging to an unidentified gene on 11q13.5 near an SNP associated with Crohn disease and atopic dermatitis. Finally, Li et al[26] sought to determine the association of candidate genes previously linked with lung function in populations of European descent to lung function in US populations. Their meta-analysis of 5 asthma populations from the NHLBI's Severe Asthma Research Program,[27,28] the Natural History of Asthma: Outcomes and Treatment Regimens study,[29,30] and the NHLBI's Collaborative Studies on the Genetics of Asthma[31] included 1441 white and African American subjects (Hispanic populations were not included). The investigators found an association of hedgehog interacting protein gene (*HHIP*) on 4q31 with lung function (FEV_1 percent predicted and forced vital capacity percent predicted) and bronchodilator reversibility but not hyperresponsiveness to methacholine.[26]

The application of new and more efficient technologies, such as whole-exome sequencing[32,33] and data mining of electronic medical records for additional and more diverse study populations,[18] promises to facilitate this research. These methodologies together underline the interdependence of basic and clinical research. In addition, various genetic studies demonstrate the possible importance of non-T_H2 mechanisms in asthma physiology and pathogenesis while emphasizing the need to identify additional phenotypic markers of such clinical processes as airway remodeling for basic gene research.[10]

Biomarkers

Biomarkers are an important link between laboratory finding and clinical relevance.[34] An ideal biomarker is minimally invasive, reproducible, and easily measured.[34] Biomarkers described in the JACI in 2011 vary widely in their characterization. Saude et al[35]

examined metabolomic profiles, the metabolic pathways and molecules created by these pathways, as a noninvasive measurement of airway dysfunction in children. These investigators found that nuclear magnetic resonance spectroscopy can identify chemical constituents of urine, and the urine metabolic profile distinguished asthmatic children with an asthma exacerbation from those with stable asthma from healthy control subjects. Kanazawa et al[36] found that pentosidine in induced sputum is a potential marker of reduced lung elasticity and collagen cross-linking in lung tissues. Pentosidine is a molecule of the extracellular matrix that accumulates with aging in connective tissues. Thus the investigators demonstrated that pentosidine is a biomarker of airway senescence and hypothesized that it might promote senescence. Sanak et al[37] profiled eicosanoids, derivatives of arachidonic acid, in exhaled breath condensate by using mass spectrometry and distinguished asthmatic from healthy control subjects; within the asthmatic group, the investigators were also able to identify those with aspirin intolerance. As reviewed by Castro et al,[38] lung imaging techniques with improved density-based, ventilation-based, or perfusion-based computed tomographic analyses or functional magnetic resonance imaging techniques or molecular imaging, have potential for defining new biomarkers. These newer imaging modalities allow both spatial and temporal resolution, thereby enabling simultaneous evaluation of anatomy and function.

Biomarkers can be used for risk stratification and prediction of disease. Urinary leukotriene E_4 levels were found to identify children with tobacco smoke exposure at risk for an asthma exacerbation.[39] Thamrin et al[40] examined fluctuations in peak expiratory flow in 2 different populations by using computer-generated probabilities to predict future exacerbations in subjects, possibly allowing a form of personalized medicine. Martin et al[32] found the presence of childhood eczema and rhinitis, a noninvasive biomarker, to be predictive of atopic asthma in middle age. The history of an asthma exacerbation in the past year is a biomarker that predicts an exacerbation in the present year.[33,40]

Bronchoscopy provides access to a range of biomarkers; it permits assessment of airway remodeling and tissue inflammation not achievable through less invasive procedures, such as collection of induced sputum. Moore et al[41] described procedures for bronchoscopy in patients with severe asthma, a group at greater risk of complications. These investigators demonstrated that bronchoscopy is relatively safe; however, 8 of 143 patients with severe and very severe asthma required inpatient evaluation after the study bronchoscopy, and 5 experienced asthma exacerbations lasting 2 to 4 days. The researchers also found that prebronchodilator FEV_1 was the strongest predictor of change in FEV_1 after bronchoscopy. Interestingly, the largest changes were observed in patients with better lung function. In other research, validation data on a noninvasive biomarker, the Asthma Impact Survey (a validated measure of the effect of asthma on biological function), were reported by Schatz et al.[42]

ENVIRONMENTAL EXPOSURES

Environmental exposures inform hypotheses for both basic science and clinical investigations. Secondhand tobacco smoke places children at increased risk for a severe exacerbation despite inhaled steroids.[39] Rabinovitch et al[39] observed that higher urinary leukotriene E_4 levels might be predictive of an asthma exacerbation among children exposed to tobacco smoke.

Exposure to traffic previously was associated with the prevalence and severity of asthma in developed countries. As reported in the JACI in 2011, Baumann et al[43] found that adolescents living in close proximity to a heavily transited roadway in a periurban shantytown in Lima, Peru, had greater risk of asthma symptoms and atopy, as measured by allergy skin testing for mite, cockroach, cat, dog, mouse, and mixed molds. The International Study on Asthma and Allergies in Childhood found Peru to have the highest prevalence of childhood asthma symptoms among the countries of Latin America.[44]

Olmedo et al[45] analyzed exposure and sensitization to indoor allergens as part of the New York City Neighborhood Asthma and Allergy Study, a case-control study among children from middle-income families living in high-asthma-prevalence neighborhoods (HAPNs) versus low-asthma-prevalence neighborhoods (LAPNs). HAPN homes had higher concentrations of cockroach, mouse, and cat antigen but lower concentrations of mite than LAPN homes. The investigators found that sensitization to cockroach was more common among children from HAPNs than among children from LAPNs. Increased exposure was associated with sensitization to cockroach, mite, and cat but not mouse or dog. These data, which were uniquely collected in a middle-income, relatively homogeneous cohort according to socioeconomic status (SES), support previous studies of the relevance of cockroach exposure.[46]

There has been much interest in the relation of exposure to farm environments to asthma prevalence. In a case-based study Omland et al[47] examined the effect on self-reported asthma of environment and occupation among rural Danish farming students and nonfarming army conscripts. The investigators found that exposure to swine and dairy stables, smoking, and welding increased the risk of asthma, although the biggest risk factor was baseline bronchial hyperresponsiveness. The investigators also found that being raised on a farm was associated with reduced risk of subsequent asthma. Atopy was not a risk factor. In a 2-time-points cross-sectional study of 1325 Hutterites of South Dakota living on communal farms,[48] asthma prevalence increased over the 10- to 13-year observation period in female subjects but not in male subjects. Atopy increased as a risk factor for asthma over the yearlong observation period. The authors hypothesized that a change in behavior (eg, in cleaning practices) or environmental exposures limited to female subjects might account for the increase in asthma.

Social exposures are also part of our environment. Psychosocial stress has been considered a "social pollutant."[49] Lange et al,[50] in a study of Puerto Rican twins, found maternal and paternal stress, including depression, to be associated with asthma hospitalizations and asthma diagnosis in twins at 1 and 3 years of age. Exposure to poverty likewise is associated with poor health and psychosocial stress. Remarkably, Sternthal et al[51] found that low maternal SES during childhood, which was defined as home ownership by her parents from the mother's birth until age 10 years, was associated with wheezing during childhood in the offspring linked through adult SES, prenatal stress, and prenatal pollution exposure. Also, low maternal childhood SES was associated with increased cord blood IgE levels. Exposure to poverty apparently has a lasting and frightening intergenerational effect.[51,52] Determining what generates resilience to poverty was the focus of a study by Chen et al[53]; the researchers

found that a shift-and-persist approach (finding the positive in such stressors and remaining optimistic and pursuing goals) protected low-SES children from detrimental asthma outcomes. Addressing poverty remains a crucial public health task.

OBESITY

The increased prevalence of obesity and its relationship to asthma is the subject of several 2011 JACI reports. Lowe et al,[54] using data from Swedish national registries, found a dose-response relationship between maternal obesity during early pregnancy and increased risk of asthma in infancy. Quinto et al[55] found that among 32,321 asthmatic children (aged 5-17 years) from Kaiser Permanente who were prescribed at least 1 asthma medication, obese children were likely to have more β-agonists and oral corticosteroids dispensed than normal-weight children. Forno et al[56] found decreased response to ICSs in overweight and obese children in a *post hoc* analysis of data from the Childhood Asthma Management Program Study. Among 1049 adults from the NHLBI-funded Severe Asthma Research Program, obese subjects with early-onset asthma (<12 years of age) had more airway obstruction and bronchial hyperresponsiveness and were more likely to have required oral steroids or had an intensive care unit admission for asthma in the preceding year.[57] Thus there is heterogeneity among subjects with asthma and obesity. Dixon et al[58] carried out a prospective study of 23 asthmatic and 21 nonasthmatic patients who underwent bariatric surgery. After surgery, asthmatic patients had improved airway responsiveness to methacholine, asthma control, and asthma quality of life.[58]

Clinical studies of asthma and obesity are now provoking an explosion of basic science investigation. Forno et al[56] hypothesize that the decreased response to steroids supports the notion that obesity is a proinflammatory state. In a preliminary study Wood et al[13] found a higher percentage of neutrophils in induced sputum and an increase in Toll-like receptor 4 gene expression in sputum cells in asthmatic patients given a high-fat meal, suggesting innate immune activation and inflammation.

MANAGEMENT

Health care costs

Asthma is expensive in terms of direct and indirect costs.[59,60] In a review of pooled data from 2003 and 2005 Medical Expenditure Panel Surveys (MEPSs) of 47,033 adults, Sullivan et al[59] reported that participants with asthma were less likely to be employed, had 1.4 more sick days, and were more likely to have activity limitations or be unable to work than participants who did not. These investigators found annual medical expenditures attributable to asthma of $18 billion, with prescription drugs the highest component of this expense; previously, hospitalizations had been the major cost.[60] Barnett and Nurmagambetov,[61] also analyzing MEPSs over 2002-2007, found that the value of additional days lost attributable to asthma per year was approximately $301 for a worker and $93 for a student. In an editorial, Gergen[60] noted that MEPS samples are subsets of National Health Interview Survey (NHIS) data. In MEPS, a subject must report a medical expenditure for asthma, and therefore the prevalence of asthma using MEPS data differs from that using the parent NHIS data, which asks only for self-report of diagnosis and symptoms. The prevalence reported in NHIS is 7.3%; when this is compared with 4.2% in the MEPS sample, it raises questions about whether asthma is for many patients so mild that a medical expenditure is not needed or whether access to a visit or prescription is beyond the reach of some patients.

Efficacy and effectiveness

Last year, research was modeled as a translational trajectory along 3 continuous and overlapping levels, as follows: T1, the translation of knowledge from the laboratory to initial studies in patients; T2, larger studies, including clinical trials, examining efficacy in patients under tightly controlled conditions; and T3, research, including comparative effectiveness research, that tests how the efficacy findings of T2 research fare in the real world in diverse populations and varied practice settings.[1,62,63] The clinical research reported in the JACI over the past year had predominantly efficacy features, with narrowly defined inclusion and exclusion criteria for study subjects and rigorous research protocols that cannot be easily implemented in the real world.[62] These T2 trials provide the first evidence that patients will benefit from the studied treatment.

Sublingual immunotherapy (SLIT) is a potentially efficacious and more convenient (effective) form of immunotherapy. Bush et al[64] randomized 31 *Dermatophagoides farinae*–sensitive adults between the ages of 18 and 50 years with allergic rhinitis, including 10 with mild intermittent asthma, to high-dose versus low-dose versus placebo SLIT. Twenty-one subjects completed the study, receiving SLIT for 12 to 18 months.[64] No severe systemic reactions occurred; there was no difference in symptom scores or medication use between groups. High-dose SLIT was associated with increased bronchial threshold to allergen challenge and increased serum *D farinae*–specific IgG_4 levels.

Tabar et al[65] demonstrated that 3 years, compared with 5 years, of specific subcutaneous immunotherapy with *Dermatophagoides pteronyssinus* is sufficient in a prospective randomized controlled trial of 239 patients with rhinitis with and without asthma.

In children with mild-to-moderate asthma participating in the Pediatric Asthma Controller Trial of the Childhood Asthma Research and Education Network, a cost-effectiveness analysis found that for children, low dose-fluticasone had lower cost and higher effectiveness than montelukast; efficacy was measured based on asthma control days, increase over baseline FEV_1 of 12% or greater, and number of exacerbations avoided.[66] A similar study is needed in a diverse cohort of adults, ideally in a pragmatic design.

In 2010, Peters et al[67] had reported that the addition of tiotropium bromide was not inferior to the addition of salmeterol to an ICS and that both tiotropium and salmeterol were superior to doubling the ICS. In 2011, Bateman et al[68] demonstrated that tiotropium is not inferior to salmeterol in 16 weeks of therapy in patients with moderate persistent asthma and the B16 Arg/Arg adrenoreceptor genotype. Kerstjens et al[69] conducted a randomized, controlled, double-blind crossover study of three 8-week treatments (5 or 10 μg of tiotropium or placebo daily) added to high-dose ICS plus long-acting β-agonist in 107 adults with severe uncontrolled asthma. The addition of tiotropium was associated with higher peak and trough FEV_1 and higher home peak expiratory flow measurements. There was no difference in bronchodilator effect between the 2 doses. Tiotropium now needs to be evaluated in T3 studies with diverse populations under real-world conditions.[62]

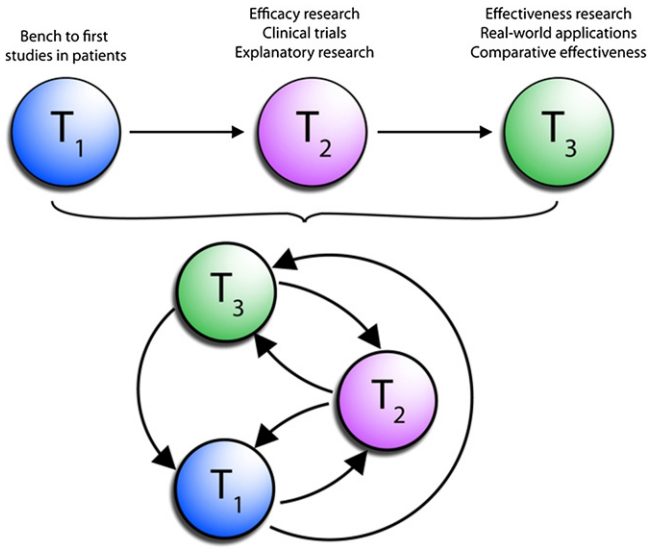

FIG 1. Last year's review depicted a linear trajectory of translation, connecting the initial studies translating bench findings to the first patients *(T_1)* to larger efficacy studies that include clinical trials studying subjects under tightly controlled conditions *(T_2)* and then to research, including comparative effectiveness research, testing how the efficacy findings of T2 research fare in the real world in diverse populations and varied practice settings *(T_3)*. This year what was observed was a more interwoven relationship (rather than a linear one) in which each translational level informs the others and new approaches to answering old questions have led to new discoveries.[1,62,63,76]

TABLE I. Key findings in the care of adults with asthma reported in the JACI in 2011

- T_H17 cytokines might promote human airway smooth muscle cell migration and might also play a supporting role in remodeling.[14]
- Pentosidine, a molecule of the extracellular matrix that accumulates with aging in connective tissues, is a biomarker of airway senescence and might promote senescence.[36]
- Low maternal SES during childhood is associated with wheezing during childhood in the offspring and increased cord blood IgE levels.[51]
- There is a dose-response relationship between maternal obesity during early pregnancy and increased risk of asthma in infancy.[54]
- High-dose *Dermatophagoides farinae* SLIT was generally tolerated in adults, some with mild intermittent asthma.[64]
- Tiotropium holds promise but needs further evaluation as an addition to standard therapy in severe uncontrolled asthma.[69]
- ICS adherence tends to increase just before and surrounding an asthma exacerbation.[74]

Corren et al[70] found that the severity of acute airway reactions and symptoms precipitated by a controlled cat-room exposure was reduced by treatment with omalizumab. Busse et al,[71] in a randomized, double-blind, placebo-controlled parallel group trial of children, adolescents, and young adults who were enrolled for 60 weeks in the Inner-City Anti-IgE Therapy for Asthma Study, found improved asthma control, decreased exacerbations, and fewer hospitalizations among the omalizumab-treated patients. A study of the cost-effectiveness of omalizumab in a pragmatic design is needed.

How medical advice is communicated and presented can influence adherence, but whether outcomes are improved is less certain.[72] Wechsler et al[73] conducted a randomized, double-blind, crossover pilot study assigning 46 adults with mild-to-moderate asthma to treatment with albuterol, placebo inhaler, sham acupuncture, or no treatment. The researchers found among the 39 subjects who completed the study that FEV_1 improved with albuterol but patient-reported improvement occurred with all treatments, more with the first 3 interventions than with no treatment.

In a pragmatic investigation, Williams et al[74] studied ICS adherence using electronic prescription and fill information in subjects aged 12 to 56 years followed, on average, for about 2 years, whose baseline FEV_1 was 87% ± 20%. The authors found that adherence increased before and around an exacerbation, which was defined as the need for oral corticosteroids, an asthma-related emergency department (ED) visit, or hospitalization; mean adherence was 26.3%. The authors estimated that 24% of exacerbations could be attributed to ICS nonadherence. Adherence was associated with a reduction in exacerbations, but this was statistically significant only in subjects whose adherence was greater than 75%.

Apter et al[75] explored whether problem solving targeted at improving electronically monitored ICS adherence compared with standard asthma education would improve adherence and asthma outcomes in adults with moderate or severe asthma mostly living in low-income urban neighborhoods and with a high prevalence of comorbidities. Baseline FEV_1 was 66% ± 19%. Although adherence decreased somewhat over the 26-week observation period, it also remained relatively good (mean, 61%) in both groups. In both of the groups asthma control improved, along with FEV_1 and quality of life, but rates of ED visits and hospitalizations did not significantly decrease. This study emphasizes the need to find ways to reduce ED visits and hospitalizations in patients with high risk of morbidity.

Needed are pragmatic trials that take account of real-world conditions with regard to how medications are used and how medical recommendations are made and interpreted and that will further inform the next basic science research (Fig 1).[1,62,63,76] Questions about therapeutics remain for which T2 clinical investigation and basic science research to unravel mechanisms are needed. For example, the safety of long-acting β-agonists is now the subject of 5 large, ongoing, randomized, double-blind, multinational trials in adults, adolescents, and children. These studies, which are being required by the US Food and Drug Administration,[4] will be as "real world" as possible and will have important end points that include asthma-related death, hospitalizations, and ED visits. There continues to be debate about how best to step up and step down asthma therapy in various settings, such as in a patient with a viral respiratory tract illness, or as a more long-term strategy.[77] These discussions, along with yearly advances in research, will eventually lead to the next version of the guidelines, as discussed by Szefler.[3]

CONCLUSION

The re-examination of old questions from new perspectives is exciting and suggests a new paradigm. Last year's theme was the linear translational trajectory from bench research (T1) to clinical trials with rigorous enrollment and protocol designs (T2) to real-world studies, including diverse populations in such settings as would be used in practice. This year's research, including key findings published in the JACI (Table I), suggests that these T1, T2, and T3 research translation components have a more interwoven relationship in which each informs the others and old questions lead to new discoveries (Fig 1). What goes around comes around.

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