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Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study

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Abstract

Patients with severe or difficult-to-treat asthma are an understudied population but account for considerable asthma morbidity, mortality, and costs. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study was a large, 3-year, multicenter, observational cohort study of 4756 patients (n = 3489 adults ≥18 years of age, n = 497 adolescents 13-17 years of age, and n = 770 children 6-12 years of age) with severe or difficult-to-treat asthma. TENOR's primary objective was to characterize the natural history of disease in this cohort. Data assessed semiannually and annually included demographics, medical history, comorbidities, asthma control, asthma-related health care use, medication use, lung function, IgE levels, self-reported asthma triggers, and asthma-related quality of life. We highlight the key findings and clinical implications from more than 25 peer-reviewed TENOR publications. Regardless of age, patients with severe or difficult-to-treat asthma demonstrated high rates of health care use and substantial asthma burden despite receiving multiple long-term controller medications. Recent exacerbation history was the strongest predictor of future asthma exacerbations. Uncontrolled asthma, as defined by the 2007 National Heart, Lung, and Blood Institute guidelines' impairment domain, was highly prevalent and predictive of future asthma exacerbations; this assessment can be used to identify high-risk patients. IgE and allergen sensitization played a role in the majority of severe or difficult-to-treat asthmatic patients.

Keywords

TENOR; severe or difficult-to-treat asthma; asthma control; asthma exacerbations; burden; medication; quality of life; allergy; IgE

Patients with severe and difficult-to-treat asthma comprise a small portion (<15%) of all asthmatic patients, yet are responsible for considerable asthma morbidity, mortality, and costs.¹⁻³ Little is known about severe or difficult-to-treat asthma and asthma-related health outcomes associated with the disease. In 2001, a multicenter, observational, prospective cohort study, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR), was initiated to study asthmatic patients described as having severe or "difficult-to-treat" disease by their physicians. The primary objective was to collect prospective data to improve the understanding of the natural history of disease in patients with severe or difficult-to-treat asthma. The secondary objectives were to examine the relationship between features of asthma treatments and outcomes, to observe the frequency of predefined comorbid conditions, and to describe the relationship between IgE levels and disease.⁴

At baseline, 4756 patients (n = 3489 adults ≥18 years of age, n = 497 adolescents 13-17 years of age, and n = 770 children 6-12 years of age) were enrolled from 283 allergy and pulmonology sites across the United States, including managed care organizations, community physicians' offices, group practices, and academic centers (see the Methods section in this article's Online Repository at www.jacionline.org for further description of sites). Patients from diverse racial/ethnic backgrounds and geographic areas were represented. TENOR study design and assessments are presented in Fig 1.^{5,6} Patients with mild or moderate asthma were eligible for enrollment if their physicians considered their asthma difficult-to-treat and they met the additional inclusion and exclusion criteria.

The baseline demographics and clinical characteristics of the TENOR cohort are presented in Table I.⁴ Female subjects accounted for 71% of adult patients and 43% and 34% of adolescents and children, respectively. The predominant race/ethnicity was white (75%), followed by black (15%) and Hispanic (6%). Mean prebronchodilator FEV₁ values were relatively high (74%, 84%, and 87% predicted for adults, adolescents, and children, respectively); however, nearly a quarter of all patients (primarily adults) had an FEV₁ of 60% or less of predicted value. Asthma severity, which was based on the physicians' subjective opinion, indicated that approximately 50% of adult and adolescent patients had severe asthma versus only 36% of children. However, nearly the entire cohort (96%) was considered to have difficult-to-treat asthma based on the need for multiple drugs, occurrence of frequent exacerbations, severe exacerbations, inability to avoid triggers, and complex treatment regimens (see Fig E1 in this article's Online Repository at www.jacionline.org).⁴ IgE levels were increased across all 3 age groups.

Difficult-to-treat asthma has introduced a relatively new dimension to more traditional definitions of severity and control, and although difficult-to-treat asthma might resonate with asthma caregivers, this asthma phenotype has not been explicitly defined in domestic and international asthma guidelines. By using the comprehensive TENOR database, which includes a wide array of both patient-reported and validated objective measures, the study has led to more than 25 peer-reviewed publications that provide insights into asthma-related health outcomes and barriers to optimal asthma care in this understudied population. Here we focus on the key lessons from TENOR in the areas of burden of illness and quality of life (QoL), asthma control and exacerbations, IgE and allergen sensitization, special populations within TENOR, clinical tools, and genetic studies.

BURDEN OF ILLNESS AND ASTHMA-RELATED QoL

High rates of health care use (HCU) and medication use were observed in the TENOR cohort. In the 3 months before enrollment, 5% and 15% of adults, 10% and 17% of adolescents, and 9% and 22% of children had at least 1 asthma hospitalization or emergency department (ED) visit, respectively, and in addition, almost half the adults and children and approximately 40% of adolescents reported oral corticosteroid (OCS) bursts and unscheduled visits for asthma.⁴ Approximately 10% of patients across all age groups reported a history of intubation for asthma. One or more school or work absences in the 2 weeks before enrollment were reported in 14% to 19% of adults, adolescents, and children. At enrollment, medication use was high: more than 55% of children (n = 450) and adolescents/adults (n = 2230) reported using 3 or more long-term asthma control medications.⁴ Commonly used long-term control medications were inhaled corticosteroids (ICSs), long-acting β -agonists, and leukotriene modifiers.^{4,7} Approximately 56% of children and 26% of adolescents/adults reported using high-dose ICSs, as defined by the American Thoracic Society refractory asthma guidelines for adults⁵ and by the National Heart, Lung, and Blood Institute (NHLBI) guidelines for children.⁶ In a separate analysis, TENOR children, adolescents, and adults were classified by asthma severity according to medication use, among other criteria for assessing asthma severity (see Tables E1-E3 in this article's Online Repository at www.jacionline.org).⁸ The level of agreement among 3 different asthma severity assessments (according to the National Asthma Education and Prevention Program guidelines, the Global Initiative for Asthma guidelines, and physician-assessed severity) was also examined and is provided in the Online Repository (see Table E4 in this article's Online Repository at www.jacionline.org).^{6,9,10}

The unmet need in patients with severe or difficult-to-treat asthma was particularly evident when examining rates of HCU in relation to long-term use of control medication across age groups. Consistently high rates of HCU were observed, despite the use of multiple long-term

controllers (Fig 2).⁷ Notably, of those using 3 or more long-term controllers, 53% of adults, 44% of adolescents, and 53% of children reported an OCS burst in the 3 months before baseline, and approximately 25% of children, 19% of adolescents, and 15% of adults reported an ED visit in the 3 months before baseline. Although the inclusion criteria for patients in the Severe Asthma Research Program, another large cohort of patients with severe asthma, differed from TENOR by including all asthma severities, data from this study also demonstrated high rates of HCU despite aggressive therapy.¹¹⁻¹⁴

LUNG FUNCTION

Because optimal control of asthma remains elusive in many children, TENOR compared the rates of asthma exacerbations by lung function in children versus adolescents/adults who were taking recommended long-term controller asthma medications.¹⁵ Zeiger et al¹⁵ showed that approximately 30% to 40% of all patients with abnormal lung function ($FEV_1 \leq 80\%$) had a course of OCSs in the 3 months before the 12- and 18-month follow-up visits (Table II). By the 24-month follow-up visit, more than half (52%) of the children had received a course of OCSs in the previous 3 months versus only 31% of adolescents/adults ($P = .02$). Approximately one quarter of all patients with normal lung function ($FEV_1 > 80\%$) received a course of OCS therapy in the 3 months before all follow-up visits. The frequency of OCS courses was significantly higher in those with abnormal than normal lung function in children at the 24-month time point and in adolescents/adults at all time points (Table III).¹⁵ With the exception of month 12 for an FEV_1 of 80% or less, the frequency of ED visits or overnight hospitalizations was significantly and clinically meaningfully higher (approximately 2- to 3-fold) in children than in adolescents/adults across both lung function strata. Medication adherence at baseline and at month 12 was not statistically significantly different across age or lung function strata; most patients (90% to 100%) self-reported regular adherence to their medication. These findings demonstrate that asthma exacerbations are frequent in patients with severe or difficult-to-treat asthma, notwithstanding treatment with multiple long-term asthma controllers, management by asthma specialists, and lung function of greater than 80% of predicted values. They also suggest that children with FEV_1 values of 80% or less might have more severe disease than adults with similar lung function.

Symptom control and response to medications

The less than optimal response to asthma medications in the TENOR cohort was further evidenced by assessing symptom control with the validated Asthma Therapy Assessment Questionnaire (ATAQ).¹⁶ Of 2942 adults examined at enrollment, 32.2% ($n = 946$) reported 3 or 4 asthma control problems¹⁷ and, compared with those with no control problems (17.0%, $n = 501$), were at greater risk for unscheduled office visits (relative risk [RR], 2.8; 95% CI, 2.4-3.2), OCS bursts (RR, 2.9; 95% CI, 2.5-3.3), ED visits (RR, 4.1; 95% CI, 2.7-6.2), or hospitalization (RR, 13.6; 95% CI, 7.4-24.9). These findings showed that poorer levels of asthma control were associated with greater risk of severe asthma-related events.

In a direct assessment of response to high-dose (500/50 μ g) and low-dose (100/50 or 250/50 μ g) fluticasone and salmeterol combination (FSC) compared with patients who never used FSC over a 2-year period, many of the adjusted asthma-related health outcomes were comparable between the high-dose FSC and the never-on-FSC group. The low-dose FSC group had significantly more favorable 24-month outcomes than the never-on-FSC group, including asthma-related QoL and asthma control (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org).¹⁸ These data suggest limited clinical benefit with high-dose FSC. They also suggest that the benefits derived from FSC were optimally achieved by using low-dose FSC and that incremental doses of FSC did not provide added clinical benefit in the population with severe or difficult-to-treat asthma. This is consistent with other studies showing a lack of dose response with FSC¹⁹⁻²¹ and supports the role of

persistent airflow limitation (PAFL), molecular mechanisms of corticosteroid resistance, a steroid-insensitive form of inflammation, or distal lung inflammation not accessible to inhaled medications in the population with difficult-to-treat asthma.

Impaired asthma-related QoL

Prospective studies evaluating the effect of asthma control on asthma-related QoL have been scarce, particularly those that assess QoL differences based on disease severity. One TENOR analysis used the Mini-Asthma Quality of Life Questionnaire²² and EuroQoL 5D²³ to assess QoL in 987 adults.²⁴ An inverse relationship was found between the number of asthma control problems and QoL: poorer control at enrollment predicted poorer QoL at follow-up. The number of asthma control problems was identified as a strong independent predictor of disease-specific QoL. General health status assessed by using the EuroQoL-5D was a better longitudinal predictor of health status than asthma severity (assessed by using the Global Initiative for Asthma guidelines¹⁰) at TENOR baseline, demonstrating that self-assessed measures of asthma control can help identify those patients at greatest risk for future health impairment.

Economic burden

TENOR analyses demonstrated that few adult patients with severe or difficult-to-treat asthma achieved control over a 2-year period, and the economic consequence of uncontrolled disease is substantial.²⁵ In this analysis, disease control was assessed using 2 approaches: (1) applying the Gaining Optimal Asthma Control criteria²⁰ and (2) using the ATAQ to identify the number of asthma control problems.

Based on the Gaining Optimal Asthma Control criteria, the majority of patients had uncontrolled asthma (83% uncontrolled, 16% inconsistently controlled, and 1.3% controlled asthma). Patients with controlled asthma experienced fewer work or school absences and less HCU than patients with uncontrolled asthma. Examining the multilevel ATAQ control score, asthma costs increased directly with the number of asthma control problems. Costs for patients with uncontrolled asthma were more than double those of patients with controlled asthma throughout the study (\$14,212 vs \$6,452, adjusted to 2002 dollars; $P < .0001$).

In children, the economic burden of severe or difficult-to-treat asthma increases with increasing impairment, and reduced impairment is associated with reduced costs. In a TENOR study with 628 children,²⁶ 61.5% had very poorly controlled (VPC) asthma, 34.9% had not well-controlled (NWC) asthma, and 3.7% had well-controlled (WC) asthma based on the 2007 NHLBI asthma guidelines' impairment domain.¹ Mean annual total asthma costs were more than twice as high in the VPC group compared with those in the NWC and WC groups (baseline: \$7846, \$3526, and \$3766, respectively; month 12: \$7326, \$2959, and \$2043, respectively; and month 24: \$8879, \$3308, and \$1861, respectively; all $P < .001$). Nearly half the total costs at baseline and month 12 and more than half the costs at month 24 were attributed to indirect costs in patients with VPC asthma. Significantly lower direct and indirect costs at each time point were observed for patients whose impairment status improved from VPC asthma after baseline and for those patients who demonstrated temporary improvement in their asthma control compared with patients who had consistent VPC asthma (see Table E5 in this article's Online Repository at www.jacionline.org).

These TENOR analyses provide additional evidence that increased attention to patients with VPC asthma, through better management strategies and more effective medications, is needed to reduce illness burden.

ASTHMA CONTROL AND EXACERBATIONS: TENOR MAIN OUTCOMES

TENOR analyses have consistently shown that a recent asthma exacerbation is the strongest predictor for a future exacerbation.^{28,29} In multivariate analyses conducted in children (n = 563), a future severe asthma exacerbation at 6 months was most strongly predicted by a recent severe exacerbation (odds ratio [OR], 3.08; 95% CI, 2.21-4.28), followed by having 3 to 4 allergic triggers (OR, 2.05; 95% CI, 1.31-3.20). Other significant predictors of future severe asthma exacerbation were race/ethnicity (OR, 1.77; 95% CI, 1.25-2.51) and having VPC asthma according to the impairment component of the NHLBI guidelines (OR, 1.59; 95% CI, 1.14-2.23).²⁸ Of the 2780 adolescents and adults aged 12 years or more analyzed, recent exacerbation was associated with increased risk of future exacerbation after 18 months (OR, 6.33; 95% CI, 4.57-8.76), even after adjustment for demographic and clinical factors, asthma severity, and asthma control.²⁹

More recently, TENOR used the criteria set forth in the impairment domain of the 2007 NHLBI guidelines²⁷ to classify asthma control and assess its association with future asthma exacerbations.³⁰ Using data representing all components of the impairment domain at enrollment, month 12, and month 24, patients were categorized into 2 groupings: VPC asthma from enrollment through 2 years of follow-up and improvement from VPC asthma at enrollment, with improvement maintained through 2 years of follow-up. In multivariate analyses, children who continued to have VPC asthma (n = 51) compared with those who improved (n = 31) over the 2-year period demonstrated a 6-fold increased risk of hospitalization, ED visit, or OCS burst (OR, 6.4; 95% CI, 1.2-34.5). Adolescent/adult patients who continued to have VPC asthma (n = 544) were more likely than those whose asthma symptoms improved (n = 181) to require an OCS burst (OR, 2.8; 95% CI, 1.7-4.8) or have a hospitalization, ED visit, or OCS burst (OR, 3.2; 95% CI, 1.9-5.3) when these outcomes were assessed as a composite measure (Fig 3).³⁰ In both age groups medication adherence did not differ between the VPC and improved from VPC asthma groups. Asthma control, as defined by the impairment domain of the 2007 NHLBI asthma guidelines, might predict future asthma exacerbations and identify high-risk patients.

Another TENOR study expanded this investigation by testing the hypothesis that components of the NHLBI impairment domain²⁷ would independently predict future asthma exacerbations and that certain components would be more effective than others in predicting risk.³¹ Among all impairment components, an exacerbation within 3 months before enrollment was the strongest independent predictor of exacerbation at the 1-year follow-up in children (OR, 2.94; $P < .001$) and adolescents/adults (OR, 2.93; $P < .001$). In children, based on short-acting β_2 -agonist use, VPC asthma was independently associated with a 2-fold increase in exacerbation risk (OR, 2.03; $P = .011$). In adolescents/adults, NWC or VPC asthma based on short-acting β_2 -agonist use (OR, 1.49), lung function (OR, 1.66), or the ATAQ score (OR, 1.94) were also independent predictors of exacerbations ($P < .001$).

IgE AND ALLERGEN SENSITIZATION

It is estimated that the population-based proportion of asthma cases attributable to atopy is between 50%-60%.^{32,33} IgE plays a key role in mediating the allergic response in asthma,³⁴ and populations of patients with asthma have increased total IgE levels compared with nonasthmatic populations. In TENOR male subjects, children, smokers, nonwhite racial/ethnic groups, and adults with childhood-onset asthma had higher IgE levels compared with nonasthmatic or nonallergic populations; total IgE levels were also associated with asthma severity in younger patients.³⁵ In groups of young TENOR patients (6-8, 9-11, 12-14, and 15-17 years of age), high frequencies of comorbid allergic diseases and allergen sensitization occurred, with reports of allergic rhinitis (AR) in approximately 75% and

atopic dermatitis (AD) in up to 25% of patients. After adjusting for age, sex, and race/ethnicity, total serum IgE levels were found to be inversely correlated with FEV₁/forced vital capacity (FVC) ratio. On the basis of this model, the predicted IgE level for an average patient with an FEV₁/FVC ratio of 70% or an FEV₁/FVC ratio of 90% was 227 and 158 IU/mL, respectively.³⁶

A high rate of skin test (ST) positivity in patients from both allergy and pulmonology practices was also observed in TENOR patients.³⁷ Of the 2561 adolescents/adults ever undergoing skin testing, nearly 94% reported being ST positive to at least 1 aeroallergen. In patients reporting a positive ST result, the prevalence of AR was significantly higher than in patients reporting a negative ST result. Similarly, there was a higher prevalence of AD in patients with a positive ST result than in patients with a negative ST result (14.8% vs 10.9%, $P < .05$). Dust, pollen, and animals were reported as asthma triggers more frequently by patients with a positive ST result ($P < .0001$ for all 3 triggers) than patients with a negative ST result. Furthermore, mold and emotional distress were more likely to be reported as asthma triggers by patients with a positive ST result than patients with a negative ST result (mold: 28.0% vs 20.6%, $P < .05$; emotional distress: 40.2% vs 36.4%, $P < .05$).

A subanalysis of adolescents/adults with IgE-mediated allergic asthma (patients with positive ST results with an IgE level of 30 to 700 IU/mL, $n = 1783$) revealed that female subjects fared worse on objective and subjective clinical measures of disease severity, including asthma-related QoL, HCU, and asthma control.³⁸ Female subjects were also more likely to report allergic comorbidities and were more susceptible to allergen-triggered asthma symptoms. The prevalence of AR was 80% in female subjects versus 74% in male subjects ($P < .05$); AD was reported in 14% of female subjects and 11% of male subjects ($P < .05$). Significantly more female subjects reported allergic asthma triggers, such as dust (82% vs 78%, $P < .05$), mold (69% vs 54%, $P < .0001$), and pet dander (61% vs 53%, $P < .01$). Physician assessment of treatment difficulty suggested that a higher proportion of female than male subjects were unable to avoid asthma triggers (43% vs 38%, $P < .05$).

SPECIAL POPULATIONS EXAMINED WITHIN TENOR

The TENOR study is unique largely because it identified important subgroups and possible asthma phenotypes within the study population, which may help improve asthma care in these groups.

Aspirin-sensitive patients

The role of aspirin-exacerbated respiratory disease as a risk factor for the development of irreversible airway obstruction was evaluated in adolescents/adults with aspirin sensitivity ($n = 459$) and those without aspirin sensitivity ($n = 2848$).³⁹ Patients with aspirin-exacerbated respiratory disease had significantly lower mean postbronchodilator percent predicted FEV₁ values and were more likely to have physician-assessed severe asthma, to have been intubated for asthma, to need OCSs, and to require higher doses of ICSs (all $P < .001$). These findings suggested that aspirin sensitivity is associated with increased asthma severity and, possibly, remodeling of both the upper and lower airways.

Older adults

Compared with 2912 younger (18-64 years) TENOR patients, 566 older (≥ 65 years)⁴⁰ patients had lower lung function (decreased prebronchodilator and postbronchodilator percent predicted FEV₁ values, $P < .001$ for each), lower HCU ($P < .05$ for all measures except hospitalizations), greater use of ICSs ($P < .05$), better reported medication adherence ($P < .001$) and overall asthma-related QoL ($P = .04$), and significantly fewer asthma control problems ($P < .001$), but reported poorer communication with physicians ($P = .02$). These

findings from studying older patients demonstrated the importance of good communication between physicians and patients and an asthma action plan, as well as appropriate use of ICSs, use of objective measures of asthma control, and adherence to a prescribed regimen.

Patients with PAFL

The cause of persistent airway obstruction in asthmatic patients is largely unknown. A 2007 TENOR analysis found that PAFL was highly prevalent in patients with severe or difficult-to-treat asthma and is associated with identifiable clinical and demographic characteristics. Adults with PAFL (postbronchodilator FEV₁/FVC ratio of <70% at 2 annual consecutive visits) were compared with subjects with normal lung function (postbronchodilator FEV₁/FVC ratio of 75% to 85%).⁴¹ Patients with chronic obstructive pulmonary disease, obesity with a restrictive respiratory pattern, or a 30 pack-year or greater history of smoking were excluded. Of 1017 TENOR patients studied, 612 (60%) showed evidence of PAFL. Risk factors for PAFL were older age (OR per 10 years, 1.4; 95% CI, 1.3-1.6), male sex (OR, 4.5; 95% CI, 2.3-8.5), black ethnicity (OR, 2.2; 95% CI, 1.3-3.8), current or past smoking (OR, 3.9 [95% CI, 1.8-8.6] and OR, 1.6 [95% CI, 1.2-2.3], respectively), aspirin sensitivity (OR, 1.5; 95% CI, 1.0-2.4), and longer asthma duration (OR per 10 years, 1.6; 95% CI, 1.4-1.8). Being Hispanic (OR, 0.44; 95% CI, 0.22-0.89) and having a higher education (OR, 0.70; 95% CI, 0.51-0.95), a family history of AD (OR, 0.56; 95% CI, 0.39-0.82), a pet or pets in the home (OR, 0.69; 95% CI, 0.51-0.94), and dust sensitivity (OR, 0.63; 95% CI, 0.43-0.91) were protective factors for PAFL. Similar to these findings, Miranda et al⁴² observed an “allergic” phenotype in patients with early-onset asthma. These patients were characterized by a positive family history of allergic comorbidities and increased airway reactivity to allergic triggers; however, these patients had better lung function. Although the precise mechanism or mechanisms by which allergy prevents PAFL are not clearly understood, it has been suggested that it might occur as the result of unique protection conferred by “inherently ‘twitchy’ airways on airway structure, mechanical force, or inflammatory and related repair.”⁴¹ Importantly, 40% of patients analyzed did not show evidence of PAFL, suggesting PAFL as a distinct asthma phenotype that might not necessarily develop in all patients with severe or difficult-to-treat asthma.

Patients with weight increase

Body mass index (BMI) and weight are positively correlated with asthma incidence and severity.⁴³⁻⁴⁵ The effects of weight change on asthma control, asthma-related QoL, number of corticosteroid bursts, and exacerbation of asthma symptoms were analyzed in 2396 TENOR adult patients.⁴⁶ Compared with patients who maintained their baseline weight or lost 5 lbs (2.27 kg) or more, those gaining 5 lbs (2.27 kg) or more during a 12-month interval reported poorer asthma control (adjusted OR, 1.22; 95% CI, 1.01-1.49; *P* = .04), worse QoL (*P* = .003), and a greater need for OCS courses (OR, 1.31; 95% CI, 1.04-1.66; *P* = .02). Strategies to prevent weight gain might improve asthma control and asthma-related QoL.

Racial disparities

Reasons underlying increased asthma morbidity and mortality in black patients compared with those from other racial/ethnic groups are not fully understood. In an analysis comparing black (*n* = 243) and white (*n* = 1885) adult TENOR patients 1 year after enrollment,⁴⁷ black patients were more likely to have (1) a higher frequency of ED visits (*P* < .001), (2) more control problems (*P* < .05), (3) poorer QoL (*P* < .05) and (4) used 3 or more long-term controllers (among those with physician-assessed severe asthma, *P* = .04).⁴⁸ These racial differences were not explained by adjustment for broad sets of confounding variables, including socioeconomic, disease severity, BMI, allergic sensitization, medication adherence, and treatment setting. Asthma-related behavioral and knowledge factors

(understudied aspects in existing racial disparity research) were also examined, but no differences between black and white patients were found, except that white patients reported more communications problems with physicians. Genetic factors, pharmacogenetic factors, or both need to be investigated as possible explanations for these racial differences.

Subspecialty differences

Subspecialty differences in 3342 TENOR patients were studied, of whom 2407 (72%) were treated by allergists and 935 (28%) were treated by pulmonologists.⁴⁹ In comparison with patients treated by allergists, those treated by pulmonologists had significantly lower socioeconomic status, more severe disease, greater use of short-acting β_2 -agonists and OCSs (among severe patients), and reported greater HCU and asthma control problems. Allergic diseases and allergen sensitizations were prevalent in patients treated by both types of subspecialists but more prevalent in allergists' patients, who were more likely to receive skin testing and immunotherapy. These differences in the characteristics of patients managed by pulmonologists and allergists need to be considered when designing and interpreting epidemiologic studies involving different specialties.

CLINICAL TOOLS

Developing reliable and predictive clinical tools may help physicians identify those patients at increased risk for hospitalization/ED visits and loss of productivity/activity. An innovative TENOR-derived risk score was developed that could reliably predict asthma-related hospitalizations/ED visits in adults with severe or difficult-to-treat asthma.⁵⁰ In an analysis of 2821 adults, 239 (8.5%) reported asthma-related hospitalizations/ED visits at follow-up. Variables that predicted increased hospitalizations/ED visits included (1) younger age; (2) female sex; (3) nonwhite ethnicity; (4) obesity (BMI ≥ 35 kg/m²); (5) postbronchodilator percent predicted FVC less than 70%; (6) history of pneumonia, diabetes, or cataracts; (7) intubation for asthma; and (8) 3 or more OCS courses in the prior 3 months. The TENOR risk score ranged from 0 to 18 (0-4, low risk; 5-7, moderate risk; and 8, high risk), which was highly predictive (c-index: 0.78) of hospitalizations/ED visits (see Table E6 in this article's Online Repository at www.jacionline.org for risk score calculation and point distribution).

The Work Productivity and Activity Impairment (WPAI) instrument is a self-reported questionnaire developed to measure health-related productivity loss.⁵¹ An allergy-specific version (WPAI:AS) was developed and tested in patients with moderate-to-severe AR.⁵² Using the TENOR database, we assessed the performance characteristics of an asthma-specific adaptation of the WPAI:AS (referred to as the WPAI:Asthma) to measure productivity loss and impairment in severe or difficult-to-treat asthma.⁵³ A disease-specific version of the WPAI is a particularly useful tool in asthmatic patients, especially among those with severe disease, which is associated with both considerable disability and indirect health costs. In the 2529 patients included, asthma control and QoL were also assessed by using the ATAQ¹⁶ and Mini-Asthma Quality of Life Questionnaire,²² respectively. Compared with patients with mild-to-moderate asthma, those with severe disease had a greater percentage of impairment at work (28% vs 14%), at school (32% vs 18%), and in daily activities (41% vs 21%). At baseline, greater asthma control problems correlated directly with higher levels of work, school, and activity impairment. A greater than 10% overall work impairment at enrollment predicted hospitalizations/ED visits at 12 months' follow-up. The WPAI:Asthma correlated with other self-reported asthma outcomes and predicted HCU at 12 months, further validating its application in assessing work and activity impairment in asthmatic patients.

GENETIC STUDIES

In the first genome-wide association analysis in patients with severe or difficult-to-treat asthma to uncover the association of DNA variants with asthma susceptibility, 473 TENOR patients and 1892 population control subjects were studied for 292,443 single nucleotide polymorphisms (SNPs) for association with asthma.⁴⁸ Total serum IgE levels, FEV₁ and FVC values, and FEV₁/FVC ratios in identified candidate regions in 473 TENOR patients and 363 control subjects without a history of asthma were also assessed. Two SNPs were found to be significantly associated with asthma: *RAD50-IL13* on chromosome 5 and *HLA-DR/DQ* on chromosome 6, with SNPs in the *RAD50* region having the strongest association with asthma traits. The *HLA-DR/DQ* regions affect T_H2 cytokine expression and antigen presentation; the *RAD50* region is involved in DNA repair. This region affects T_H2 cytokine expression in mice and might have a functional role in human asthma. These findings suggest that variants in *RAD50* or closely surrounding genes (*IL13* or *IL4*) of that locus should be considered potential genetic markers of disease for future studies in patients with severe asthma or perhaps even children with asthma at risk for severe asthma.

CONCLUSIONS

Since its launch in 2001, TENOR has provided the scientific and clinical community with important lessons in understanding the natural history, asthma morbidity and burden, and unmet needs in patients with severe or difficult-to-treat asthma for the purpose of improving asthma-related health outcomes in this understudied population. The key observations and clinical implications from TENOR have potentially important clinical implications for health care providers (Table IV).^{*} It should be noted that findings from TENOR are representative of specialist care in the United States and might not be representative of asthma in the general population or of asthmatic patients in primary care practices. Also, there was no direct measure of medication adherence collected in TENOR; adherence was analyzed by using a question from the ATAQ¹⁶ instrument as a proxy.

All patients with difficult-to-treat asthma should be carefully assessed for recent exacerbation history, the strongest predictor for future asthma exacerbations,^{28,29} a recommendation that has been incorporated into the risk domain of the most recent NHLBI asthma guidelines.²⁷ In addition, asthma control, as defined by the NHLBI guidelines' impairment domain, is highly predictive of future asthma exacerbations and can be used to identify high-risk patients. Validated instruments, such as the ATAQ, can help identify those patients at particular risk for future health impairment. Physicians should also examine patients' lack of response to current medications, particularly those patients receiving multiple long-term controller medications, which might signal the need for changes in management. Use of improved management strategies, more effective medications, or both, in patients with poorly controlled asthma might significantly reduce the clinical and cost burden of asthma. Clinicians and health care workers should be aware of patients in specific high-risk groups: older patients (≥ 65 years), those with aspirin sensitivity, smokers, patients with a history of PAFL, and particularly black patients, who have a predisposition for severe asthma⁵⁴ with compromised responsiveness to some medications. Allergen STs and total IgE levels should be considered important aspects of patients' assessments. Physicians should be aware of the tenets of good communication, a clearly stated action plan, appropriate use of ICSs, objective measures of asthma control, and adherence to prescribed treatment regimens. Strategies to prevent weight gain can help patients achieve better asthma control and improve asthma-related QoL.⁴⁶ Finally, treatment patterns between allergists and pulmonologists are linked to underlying differences in demographic and

^{*}References 4, 7, 8, 15, 17, 18, 24-26, 28-31, 35-41, and 47-50.

clinical factors, which should be taken into account when designing and interpreting epidemiologic studies. We hope to restudy the TENOR cohort after 10 years to further our understanding of the natural history of severe or difficult-to-treat asthma and improve the management of those asthmatic patients with the greatest clinical and cost burden.

METHODS

TENOR sites were evenly distributed across the 4 main census regions (Northeast, South, Midwest, and West), with 27% of sites contributing less than 10 patients, 32% of sites contributing 10 to 19 patients, and 42% of sites contributing 20 or more patients. The 10 largest sites enrolled 40 to 46 patients.

We compared cumulative costs for patients who had consistently VPC asthma at baseline, 12 months, and 24 months (VPC-VPC-VPC) with costs for patients whose symptoms improved and remained improved. Four improvement categories were defined by improvement from baseline to 12 and 24 months and were compared with the consistently VPC group: improvement to NWC asthma at 12 months and continuing to have NWC asthma at 24 months (VPC-NWC-NWC), improvement to NWC asthma at 12 months and continuing to have WC asthma at 24 months (VPC-NWC-WC), improvement to WC asthma at 12 months but reverting to NWC asthma at 24 months (VPC-WC-NWC), and improvement to WC asthma at 12 months and continuing to have WC asthma at 24 months (VPC-WC-WC). We also examined patients who demonstrated temporary improvement to NWC or WC asthma at 12 months but reverted back to VPC asthma at 24 months (VPC-NWC-VPC and VPC-WC-VPC). The results for this group should be interpreted with caution because of the small sample size ($n = 18$).

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Abbreviations used

AD	Atopic dermatitis
AR	Allergic rhinitis
ATAQ	Asthma Therapy Assessment Questionnaire
BMI	Body mass index
ED	Emergency department
FVC	Forced vital capacity
FSC	Fluticasone and salmeterol combination
HCU	Health care use
ICS	Inhaled corticosteroid

NHLBI	National Heart, Lung, and Blood Institute
NWC	Not well controlled
OCS	Oral corticosteroid
OR	Odds ratio
PAFL	Persistent airflow limitation
QoL	Quality of life
RR	Relative risk
SNP	Single nucleotide polymorphism
ST	Skin test
TENOR	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
VPC	Very poorly controlled
WC	Well controlled
WPAI	Work Productivity and Activity Impairment

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FIG 1.
TENOR study design. *Daily high doses of inhaled steroids were defined by the American Thoracic Society refractory asthma guidelines for adults⁵ and by the NHLBI guidelines for children.⁶ AEs, Adverse events.

FIG 2.

Rates of HCU by number of long-term controller medications in patients aged 6 to 11 years (*left panel*), 12-17 years (*center panel*), and 18 or more years (*right panel*). Long-term controllers included ICSs, long-acting β -agonists, leukotriene modifiers, methylxanthines, and cromolyn sodium or nedocromil. No statistically significant differences were found in rates of HCU by number of long-term controllers in children and adolescents; * $P < .01$ for all HCU measures in adults except history of intubation, which was not significant.⁷

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FIG 3.

Risk of asthma exacerbations at the month 30 visit associated with consistently VPC asthma, as defined by the impairment domain of the NHLBI guidelines. Final adjusted models for hospitalizations and ED visits include prior hospitalizations or ED visits, number of long-term controllers, BMI, allergic triggers, nonallergic triggers, percent predicted FVC, race/ethnicity, and age. Final adjusted models for corticosteroid bursts include prior corticosteroid burst, chronic obstructive pulmonary disease, nonallergic triggers, percent predicted FEV₁/FVC ratio, race/ethnicity, and age.³⁰ Reprinted from Haselkorn et al,³⁰ Copyright (2009), with permission from Elsevier.

FIG E1.
Physician assessment of treatment difficulty.

FIG E2.

Least mean square difference and 95% confidence intervals (low-dose salmeterol/fluticasone combination [SFC] minus never-on-SFC: high-dose SFC minus never-on-SFC) in mean Mini Asthma Quality of Life Questionnaire (miniAQLQ) overall scores at 24 months. [#]Baseline differences between treatment groups, including severity differences, were adjusted with propensity scores; ¶quality of life (QoL) 0.40, $P = .0015$; +QoL 0.20, $P = .0456$; §QoL 0.23, $P = .0672$; ^fQoL 0.01, $P = .8915$.

FIG E3.

Least mean square difference and 95% confidence intervals (low-dose salmeterol/fluticasone combination [SFC] minus never-on-SFC; high-dose SFC minus never-on-SFC) in mean Asthma Therapy Assessment Questionnaire (ATAQ) scores at 24 months. [#]Baseline differences between treatment groups, including severity differences, were adjusted with propensity scores; ¶asthma control -0.46, $P < .0001$; +asthma control -0.33, $P = .0018$; §asthma control 0.18, $P = .1328$; f_{asthma control} -0.04, $P = .7428$.

TABLE I

TENOR baseline demographics and clinical characteristics⁴

Variable	Adults (≥ 18 y)	Adolescents (13-17 y)	Children (6-12 y)
Patients, no. (%)	3489 (73.36)	497 (10.45)	770 (16.19)
Age (y), mean ± SD	48.9 ± 14.85	14.5 ± 1.34	9.5 ± 1.88
Weight (kg), mean ± SD	83.9 ± 2.22	66.9 ± 21.03	41.1 ± 16.64
BMI (kg/m ²), mean ± SD	30.4 ± 7.73	25.4 ± 9.86	20.7 ± 6.17
IgE (IU/mL), geometric mean	85.2	223.8	182.5
Sex, no. (%)			
Female	2475 (71.2)	213 (42.9)	257 (33.5)
Male	999 (28.8)	283 (57.1)	510 (66.5)
Race/ethnicity, no. (%)			
White	2769 (79.8)	323 (65.4)	463 (60.4)
Black	404 (11.6)	115 (23.2)	193 (25.2)
Hispanic	197 (5.7)	36 (7.3)	70 (9.1)
Asian or Pacific Islander	57 (1.6)	7 (1.4)	8 (1.0)
Other	44 (1.2)	14 (2.8)	33 (4.3)
Physician's assessment of severity, no. (%)			
Mild	91 (2.6)	19 (3.8)	39 (5.1)
Moderate	1585 (46.1)	237 (47.9)	453 (59.1)
Severe	1771 (51.2)	239 (48.3)	275 (35.9)
Smoking history, no. (%)			
Never smoked	2,207 (63.7)	483 (97.8)	764 (99.6)
Past smoker	1110 (32.0)	3 (0.6)	0
Current smoker	148 (4.3)	8 (1.6)	3 (0.4)
FEV ₁ , no. (%) with predicted bronchodilator			
60%	893 (27.8)	69 (15.7)	53 (8.0)
>60% to <80%	1015 (31.6)	104 (23.7)	173 (26.0)
80%	1302 (40.6)	266 (60.6)	439 (66.0)
Prebronchodilator (% predicted), mean ± SD	74.2 ± 23.45	84.0 ± 21.63	87.0 ± 19.57
Postbronchodilator (% predicted), mean ± SD	79.0 ± 23.08	91.1 ± 21.03	93.9 ± 18.50
QoL, * mean overall score	4.6	5.2	5.4

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NA, Not applicable.

Questionnaire in patients 13 years or older and the Pediatric Asthma Quality-of-Life

Questionnaire with Standardized Activities in patients aged 6 to 12 years.

* Asthma-related QoL was measured with the Juniper Mini Asthma Quality-of-Life

Frequency of exacerbation outcomes in children aged 6 to 11 years and adolescents and adults aged 12 years and older stratified by lung function¹⁵

TABLE II

	FEV ₁ (% predicted 80%)		FEV ₁ (% predicted >80%)		P value [*]
	Age 6-11 y (n = 34)	Age 12 y (n = 1081)	Age 6-11 y (n = 187)	Age 12 y (n = 645)	
ED visit or hospitalization (%)					
12 mo	14.7	9.9	11.3	5.9	.01
18 mo	23.1	8.8	11.9	5.4	.004
24 mo	22.2	8.7	13.4	5.1	.001
OCS course (%)					
12 mo	41.2	36.4	26.3	24.1	.53
18 mo	26.9	31.4	22.8	21.8	.80
24 mo	51.9	30.7	26.1	22.6	.39

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^{*} P values compare differences between age groups.

[†] Derived from the Fisher exact test; other P values were derived from the Pearson χ^2 test.

TABLE III

Frequency of exacerbation outcomes in lung function groups stratified by children aged 6 to 11 years and adolescents and adults aged 12 years and older¹⁵

	Age 6-11 y			Age 12 y				
	FEV ₁ % predicted	80% (n = 34)	FEV ₁ % predicted >80% (n = 187)	P value *	FEV ₁ % predicted	80% (n = 1081)	FEV ₁ % predicted >80% (n = 645)	P value *
ED visit or hospitalization (%)								
12 mo	14.7		11.3	.57 [†]		9.9	5.9	.004
18 mo	23.1		11.9	.13 [†]		8.8	5.4	.01
24 mo	22.2		13.4	.24 [†]		8.7	5.1	.02
OCS course (%)								
12 mo	41.2		26.3	.08		36.4	24.1	<.001
18 mo	26.9		22.8	.64		31.4	21.8	<.001
24 mo	51.9		26.1	.007		30.7	22.6	.001

* P values compare differences between lung function groups.

[†] Derived from the Fisher exact test; other P values were derived from the Pearson χ^2 test.

TABLE IV

Key observations and applications to patient care from TENOR

Key TENOR observations and applications	Reference
I. Key observations from the cohort	
Asthma treatments that prevent loss of lung function and reduce health care resource use are needed.	Dolan et al, 2004 ⁴ Chipps et al, 2007 ⁷ Zeiger et al, 2009 ¹⁵
Poor response to asthma medications might contribute to disproportionately high asthma morbidity and mortality, underscoring our need to find more effective treatment regimens in these patients.	Dolan et al, 2004 ⁴ Chipps et al, 2007 ⁷ Campbell et al, 2008 ¹⁸
Use of improved management strategies, more effective medications, or both in patients with poorly controlled asthma can significantly reduce the clinical and cost burden of asthma.	Sullivan et al, 2007 ²⁵ Haselkorn et al, 2009 ³⁰ Szefer et al, 2011 ²⁶
Aspirin sensitivity is associated with increased asthma severity and possible remodeling of the lower airways.	Mascia et al, 2005 ³⁹
Blacks are predisposed to severe asthma, increased risk of asthma exacerbations, and compromised responsiveness to some medications.	Miller et al, 2007 ²⁹ Haselkorn et al, 2008 ⁴⁷ Haselkorn et al, 2009 ²⁸
Subspecialty practice patterns are linked to underlying differences in socioeconomic status, asthma severity, use of medications, pattern of HCU, and atopic disease.	Chen et al, 2008 ⁴⁹
High asthma costs are associated with VPC asthma and decrease with improvement in control.	Sullivan et al, 2007 ²⁵ Szefer et al, 2011 ²⁶
Female patients with IgE-mediated allergic asthma fare worse than male subjects on objective and clinical measures of disease severity, including QoL, HCU, and asthma control, and have higher rates of allergic comorbidities.	Lee et al, 2006 ³⁸
In patients with severe or difficult-to-treat asthma, the <i>RAD50-IL13</i> and <i>HLA-DR/DQ</i> regions might be associated with asthma susceptibility, as confirmed by GWAS.	Li et al, 2010 ⁴⁸
II. Applications to patient care	
Recent exacerbation history should be included as a component of asthma assessment and management plans.	Miller et al, 2007 ²⁹ Haselkorn et al, 2009 ²⁸ Zeiger et al, 2012 ³¹
Physicians can use a validated, self-assessed measure of asthma control in patients to identify and manage those at greatest risk for future health impairment and severe asthma-related events.	Sullivan et al, 2007 ¹⁷ Chen et al, 2007 ²⁴
Defining asthma control by the impairment domain of the 2007 asthma guidelines can help clinicians predict future exacerbations in individual patients.	Haselkorn et al, 2009 ³⁰
Clinical assessment of asthma severity should consider a patient's medication use and consumption of health care resources for asthma exacerbations.	Miller et al, 2005 ⁸
Physicians should be aware of patients who might be at risk for PAFL.	Lee et al, 2007 ⁴¹
Measurement of total serum IgE levels and evaluation of allergic sensitization should be considered important aspects of asthmatic patients' assessments.	Borish et al, 2005 ³⁵ Haselkorn et al, 2006 ³⁷ Lee et al, 2006 ³⁸ Haselkorn et al, 2010 ³⁶
Physicians should be aware of the tenets of good communication, a clearly stated action plan, appropriate use of ICSs, objective measures of asthma control, and adherence to prescribed regimens.	Slavin et al, 2006 ⁴⁰
Special attention should be given to patients with aspirin sensitivity.	Mascia et al, 2005 ³⁹
Strategies to prevent weight gain might help patients achieve better asthma control and improve asthma-related QoL.	Haselkorn et al, 2006 ³⁷
The TENOR risk score is a clinically useful tool for assessing the likelihood of asthma-related hospitalization or ED visits in adults with severe or difficult-to-treat asthma.	Miller et al, 2006 ⁵⁰
The WPAI:Asthma correlates significantly with multiple other asthma-related outcomes both at baseline and longitudinally and provides a simple, self-reported means of measuring the effect of asthma on productivity and impairment.	Chen et al, 2008 ⁴⁹

GWAS, Genome-wide association study.

TABLE E1

Classification of TENOR patients according to asthma severity category: children 6 to 11 years of age (n = 521)

	Asthma severity criteria		
	Mild	Moderate	Severe
Symptoms alone, no. (%)	257 (49.3)	91 (17.5)	173 (33.2)
Lung function alone, no. (%)	351 (67.4)	132 (25.3)	38 (7.3)
NAEPP, no. (%)	187 (35.9)	141 (27.1)	193 (37.0)
Medications alone, no. (%)	50 (9.6)	194 (37.2)	277 (53.2)
GINA, no. (%)	26 (5.0)	139 (26.7)	356 (68.3)
Physician assessment, no. (%)	27 (5.2)	316 (60.7)	178 (34.2)

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GINA, Global Initiative for Asthma; *NAEPP*, National Asthma Education and Prevention Program.

TABLE E2

Classification of TENOR patients according to asthma severity category: adolescents aged 12 to 18 years (n = 522)

	Asthma severity criteria		
	Mild	Moderate	Severe
Symptoms alone, no. (%)	283 (54.2)	80 (15.3)	159 (30.5)
Lung function alone, no. (%)	306 (58.6)	136 (26.1)	80 (15.3)
NAEPP, no. (%)	181 (34.7)	138 (26.4)	203 (38.9)
Medications alone, no. (%)	54 (10.3)	304 (58.2)	164 (31.4)
GINA, no. (%)	21 (4.0)	211 (40.4)	290 (55.6)
Physician assessment, no. (%)	16 (3.1)	265 (50.8)	241 (46.2)

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GINA, Global Initiative for Asthma; *NAEPP*, National Asthma Education and Prevention Program.

TABLE E3

Classification of TENOR patients according to asthma severity category: adults aged 19 to 55 years (n = 1884)

	Asthma severity criteria		
	Mild	Moderate	Severe
Symptoms alone, no. (%)	931 (49.4)	347 (18.4)	606 (32.2)
Lung function alone, no. (%)	879 (46.7)	576 (30.6)	429 (22.8)
NAEPP, no. (%)	482 (25.6)	556 (29.5)	846 (44.9)
Medications alone, no. (%)	201 (10.7)	1155 (61.3)	528 (28.0)
GINA, no. (%)	62 (3.3)	755 (40.1)	1067 (56.6)
Physician assessment, no. (%)	45 (2.4)	872 (46.3)	967 (51.3)

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TABLE E4

Concordance between asthma severity assessments in TENOR (n = 2927)

	Physician assessment			
	Mild, no. (%)	Moderate, no. (%)	Severe, no. (%)	Total, no. (%)
NAEPP [*]				
Mild, no. (%)	51 (1.7)	551 (18.8)	248 (8.5)	850 (29.0)
Moderate, no. (%)	19 (0.7)	475 (16.2)	341 (11.7)	835 (28.5)
Severe, no. (%)	18 (0.6)	427 (14.6)	797 (27.2)	1242 (42.4)
Total, no. (%)	88 (3.0)	1453 (49.6)	1386 (47.4)	2927 (100.0)
GINA [†]				
Mild, no. (%)	13 (0.4)	76 (2.6)	20 (0.7)	109 (3.7)
Moderate, no. (%)	50 (1.7)	699 (23.9)	356 (12.2)	1105 (37.8)
Severe, no. (%)	25 (0.9)	678 (23.2)	1010 (34.5)	1713 (58.5)
Total, no. (%)	88 (3.0)	1453 (49.6)	1386 (47.4)	2927 (100.0)

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GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program.

^{*} Weighted κ value for physician's assessment versus National Asthma Education and Prevention Program = 0.20 (95% CI, 0.177-0.224).

[†] Weighted κ value for physician's assessment versus Global Initiative for Asthma = 0.25 (95% CI, 0.219-0.281).

TABLE E5

Mean annual number of HCU visits and costs by longitudinal asthma control status*

	Baseline				Month 12				Month 24			
	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]
Direct asthma costs												
Physician's office visits												
No.	56	18	37		56	18	37		56	18	37	
Mean (SD)	13.4 ± 10.6	8.7 ± 10.1	8.4 ± 6.3	.10, .012, .92	9.9 ± 7.1	4.7 ± 3.9	4.4 ± 2.9	.004, <.001, .80	8.4 ± 6.9	5.6 ± 8.5	4.8 ± 4.0	.15, .005, .64
Subcost (\$)	1,033.58	670.63	652.50		768.27	361.11	342.98		652.20	429.89	368.08	
95% CI subcost (\$)	845-1,233	376-1,063	497-815		626-900	232-500	270-416		511-793	190-810	264-472	
Hospital nights												
No.	56	18	37		56	18	37		56	18	37	
Mean (SD)	2.6 ± 8.1	1.3 ± 4.1	0.0 ± 0.0	.51, .050, .052	1.1 ± 3.0	0.0 ± 0.0	0.0 ± 0.0	.12, .025, —	3.3 ± 8.3	0.0 ± 0.0	0.3 ± 1.4	.10, .036, .32
Subcost (\$)	1,943.85	980.68	0.00		814.31	0.00	0.00		2,390.41	0.00	238.54	
95% CI subcost (\$)	623-3,637	0-2,522	0-0		305-1,430	0-0	0-0		989-4,047	0-0	0-592	
ED visits												
No.	56	18	37		56	18	37		56	18	37	
Mean (SD)	2.4 ± 3.6	0.9 ± 2.2	0.4 ± 1.6	.088, .002, .38	1.2 ± 1.8	0.1 ± 0.5	0.2 ± 0.6	.013, .002, .53	1.5 ± 2.7	0.3 ± 0.8	0.5 ± 1.1	.079, .035, .60
Subcost (\$)	708.97	259.49	126.24		354.49	32.44	63.12		437.90	97.31	142.02	
95% CI subcost (\$)	467-982	0-556	0-292		226-494	0-103	15-131		245-643	0-209	51-251	
Mean drug cost [‡]	2,474.70	2,145.79	2,088.59	<.001, <.001, .63	2,509.31	2,013.18	1,996.75	<.001, .002, .91	2,450.32	2,146.81	1,909.15	.098, <.001, .25
95% CI cost (\$)	2,326-2,626	1,962-2,306	1,905-2,259		2,347-2,680	1,821-2,209	1,780-2,187		2,288-2,625	1,816-2,447	1,702-2,106	
Mean direct cost [¶]	6,161.10	4,056.59	2,867.33	.11, <.001, .27	4,446.38	2,406.72	2,402.85	<.001, <.001, .98	5,930.83	2,674.01	2,657.79	<.001, <.001, .91
95% CI subcost (\$)	4,689-8,081	2,580-6,228	2,535-3,192		3,817-5,211	2,130-2,701	2,154-2,649		4,269-7,852	2,237-3,110	2,198-3,177	
Indirect asthma costs												
School days lost												
No.	44	17	32		47	17	34		46	18	35	
Mean (SD)	16.4 ± 44.0	0.0 ± 0.0	26.8 ± 50.2	.13, .34, .033	13.6 ± 43.3	0.0 ± 0.0	3.8 ± 12.9	.20, .21, .23	20.2 ± 52.0	20.2 ± 47.7	0.0 ± 0.0	.99, .024, .014

	Baseline			Month 12			Month 24					
	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]	Consistently VPC asthma (n = 56) [a]	Temporary improvement (n = 18) [b]	Improved from VPC asthma (n = 37) [c]	P value [†] : [a] vs [b], [a]vs [c], [b]vs [c]
95% CI subcost (\$) ^{//}	879-5,466	0-0	1,635-7,794		647-4,818	0-0	0-1,547		1,131-6,187	0-7,712	0-0	
Mean indirect cost	2,826.64	0.00	4,621.94		2,336.30	0.00	659.10		3,483.20	3,485.91	0.00	
95% CI subcost (\$)	879-5,466	0-0	1,635-7,794		647-4,818	0-0	0-1,547		1,131-6,187	0-7,712	0-0	
Mean total asthma cost ^{\$}	8,963.77	4,138.05	7,534.49	.012, 0.48, .082	6,977.91	2,333.04	3,034.50	<.001, <.001, .12	9,399.39	6,159.91	2,640.95	.27, <.001, .082
95% CI cost (\$)	6,310-12,111	2,577-6,446	4,508-10,853		5,055-9,514	2,079-2,618	2,239-4,104		6,046-13,237	2,441-10,684	2,164-3,197	

^{*}Table E5 is based on the number of patients who were in either the consistently VPC asthma (n = 56), improved from VPC asthma (n = 37), or temporary improvement (n = 18) groups. Burden and associated costs were calculated per year for each measure.

[†]Significance was assessed by using the Student *t* test for each pairwise comparison of units. Significance of costs assessed by computing 1-tailed *P* values based on the proportion of bootstrap samples with positive differences and multiplying by 2 to obtain a 2-tailed *P* value.

[‡]Drug costs included ICSs, OCSs/systemic corticosteroids, short- and long-acting β-agonists, methylxanthines, cromolyns, and leukotriene modifiers.

[§]Mean total cost includes variables relating to indirect (productivity loss) and direct (HCU and medication use) costs. Mean costs of the 2 components do not sum to the total because they are only for patients with both components.

^{//}CI's are based on 1000 bootstrap samples.

[¶]Direct costs include costs from HCU and medication use.

TABLE E6

TENOR risk score calculation, point distribution, and proportion of patients with hospitalizations or ED visits after baseline

Points	Variable	All original population subjects (n = 2821), no. (%)	Subjects with hospital/ED visit, no. (%)
3	Age (y)		
	0: 60	720 (25.5)	31 (4.3)
	1: 50-59	678 (24.0)	45 (6.6)
	2: 35-49	981 (34.8)	103 (10.5)
	3: 18-34	442 (15.7)	60 (13.6)
1	Sex		
	0: Male	800 (28.4)	43 (5.4)
	1: Female	2021 (71.6)	196 (9.7)
2	Race/ethnicity		
	0: White	2278 (80.8)	144 (6.3)
	2: Nonwhite	543 (19.2)	95 (17.5)
1	BMI (kg/m ²)		
	0: <35	2132 (75.6)	141 (6.6)
	1: 35	689 (24.4)	98 (14.2)
2	Lung function		
	0: Post % predicted FVC ≥ 70%	2396 (84.9)	173 (7.2)
	2: Post % predicted FVC <70%	425 (15.1)	66 (15.5)
1	Previous history of pneumonia		
	0: No history	1122 (39.8)	55 (4.9)
	1: Previous history	1699 (60.2)	184 (10.8)
1	Currently has diabetes		
	0: No	2612 (92.6)	205 (7.9)
	1: Yes	209 (7.4)	34 (16.3)
1	Currently has cataracts		
	0: No	2461 (87.2)	199 (8.1)
	1: Yes	360 (12.8)	40 (11.1)
1	Ever intubated (ventilator use)		
	0: No	2474 (87.7)	183 (7.4)
	1: Yes	347 (12.3)	56 (16.1)
3	Steroid bursts in last 3 mo		
	0: No steroid bursts	1476 (52.3)	72 (4.9)
	1: 1 Steroid burst	709 (25.1)	58 (8.2)
	2: 2 Steroid bursts	358 (12.7)	44 (12.3)
	3: 3 or more steroid bursts	278 (9.9)	65 (23.4)
1	Nebulizer ipratropium bromide		
	0: No	2663 (94.4)	211 (7.9)
	1: Yes	158 (5.6)	28 (17.7)
1	Systemic corticosteroids		

Points	Variable	All original population subjects (n = 2821), no. (%)	Subjects with hospital/ED visit, no. (%)
	0: Less than every other day	2336 (82.8)	161 (6.9)
	1: At least every other day	485 (17.2)	78 (16.1)
18	Total possible score		