WHITEPAPER

Severe Asthma and Blood Eosinophils: A Retrospective Cohort Analysis Using Electronic Health Records

John Farah, PhD
Alan Wilk, BS
Kevin Lavelle, BS
Nam Nguyen, MS
Joe Vasey, PhD
Lee Kallenbach, PhD

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ABBREVIATIONS

ACCP	American College of Chest Physicians
ACT	Asthma Control Test™
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
CY	Calendar Year
DHHS	(US) Department of Health and Human Services
EHR	Electronic Health Record
ERS	European Respiratory Society
FDA	Food and Drug Administration
GINA	Global Initiative for Asthma
HCP	Healthcare Provider
ICD-9	International Classification of Disease-Ninth Revision
ICD-10	International Classification of Disease-Tenth Revision
ICS	Inhaled Corticosteroid
IL (-4, -5, -13)	Interleukin (-4, -5, -13)
IgE	Immunoglobulin E
LABA	Long-Acting $Beta_2$-Agonist
LAMA	Long-Acting Muscarinic Antagonists
mAb	Monoclonal antibody
MCID	Minimally Clinically Important Difference
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NLM	National Library of Medicine
NLP	Natural Language Processing
OCS	Oral Corticosteroids
PROM	Patient-Reported Outcome Measure
RCT	Randomized Clinical Trial
RWD	Real-World Data
RWE	Real-World Evidence
SABA	Short-Acting $Beta_2$-Agonist
SAMA	Short-Acting Muscarinic Antagonists
SD	Standard Deviation
TENOR	The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens
US	United States
UK	United Kingdom

EXECUTIVE SUMMARY

Asthma, a complex respiratory disease characterized by airway inflammation, airflow limitation, and bronchial hyper-responsiveness, is estimated to affect 25 million Americans. The clinical burden and economic costs of asthma are substantial and correlate closely with disease severity. Approximately 5% to 10% of patients have severe asthma that remains uncontrolled or is only partially controlled despite adherence to standard treatment. Severe uncontrolled asthma varies among patients with respect to presentation, treatment response, and clinical outcomes. Characterizing patients according to observable traits (phenotype) and pathobiologic mechanisms (endotype) has the potential to personalize asthma management through a biomarker-driven approach that enables accurate diagnosis and effective use of standard and targeted therapies.

This paper reviews the management and pharmacologic treatment of severe asthma and describes eosinophilic asthma, a subtype associated with frequent exacerbations of symptoms and poor prognosis that accounts for up to one-half of severe cases. Next, we consider how real-world observations may offer insight into the challenges and opportunities associated with uncontrolled asthma. Using de-identified ambulatory patient data sourced from Practice Fusion a Veradigm™ EHR to generate actionable real-world evidence, we characterized patients who required additional therapy for control of asthma symptoms and evaluated how blood eosinophil levels affected personalization of asthma care. More than one-half of patients had evidence of persistent severe asthma. Asthma Control Test™ scores suggested asthma was not well controlled for a substantial proportion of patients completing the test. Over 25% of patients had blood eosinophil counts greater than or equal to a threshold associated with increased healthcare utilization and disease burden that may identify patients who are likely to benefit from therapies targeting type 2 inflammation. The retrospective analysis suggests opportunities exist for consideration of biologics for patients in whom eosinophils play a pathobiologic role. Studies that leverage real-world data from electronic health platforms may inform innovative therapeutics and provide insight into eosinophilic asthma, other subtypes of severe asthma, and treatment effectiveness in support of care plans tailored to individual patients.

INTRODUCTION

Asthma is a complex respiratory disease characterized by airway inflammation, expiratory airflow limitation, and bronchial hyper-responsiveness. Symptoms often include coughing, wheezing, chest tightness, and shortness of breath. In the United States (US), 25 million individuals (~19 million adults and ~6 million children) are estimated to have asthma; worldwide, as many as 339 million individuals may be affected (CDC 2019; Global Asthma Network, 2018). Uncontrolled asthma is associated with significant clinical burden, diminished quality of life, and increased healthcare utilization. In 2013, direct and indirect costs of treated asthma (15.4 million individuals) in the US approached $82 billion (Nurmagambetov et al. 2018). Over the next two decades, adults and adolescents will lose an estimated 15 million quality-adjusted life years owing to uncontrolled asthma (Yaghoubi et al. 2019).

Morbidity and economic burden of asthma correlate closely with asthma severity.

- Approximately 5% to 10% and possibly up to 20% of patients with asthma have severe or uncontrolled disease (Wenzel 2004; Chung et al. 2014; Bleecker and Castro 2019).
- As defined by the European Respiratory Society (ERS)/American Thoracic Society (ATS) Task-force, severe asthma "requires treatment with high-dose inhaled corticosteroids plus a second therapy and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy" (Chung et al. 2014).
- The Global Initiative for Asthma (GINA), a collaborative effort between the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO), defines severe asthma as a subset of difficult-to-treat asthma that is "uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased." Asthma is not severe if it improves when adherence and inhaler technique are optimized (GINA 2019b).
- A retrospective analysis of US claims data reported patients with severe asthma had frequent exacerbations—sudden worsening of asthma symptoms due to bronchoconstriction—and 2.9-fold higher adjusted asthma-related costs despite greater use of asthma medications and better adherence to controller therapy than patients with persistent but not severe asthma (Chastek et al. 2016).
- In another report of two retrospective cohort studies that evaluated patients from the US and the United Kingdom (UK), increased disease severity was associated with a higher frequency and greater risk of exacerbations and with higher rates of emergency department and hospital readmission (Suruki et al. 2017).
- Although severe asthma affects a small proportion of the total asthma population, much of the morbidity and mortality associated with asthma and at least one-half of all asthma-related healthcare costs have been ascribed to severe asthma (ACCP 2018; Zervas et al. 2018).

Severe asthma varies among patients with respect to presentation and outcomes.

- Diverse symptom profiles and variable responses to specific pharmacotherapies are evident across the entire severe asthma spectrum (Moore et al. 2013).
- Genetic and epigenetic variability and environmental exposure may explain much of the heterogeneity between individuals; these factors drive pathobiologic mechanisms (endotype) that underlie the observable traits (phenotype) encountered in clinical settings (Wenzel 2012; Carr and Bleecker 2016).
- Characterizing patients according to phenotype and/or endotype has the potential to transform personalized asthma management, especially for adherent patients who have suboptimal outcomes using standard controller and relief pharmacotherapies (Wenzel 2012; Lotvall et al. 2011; Heffler et al. 2018).
- The identification of clinically meaningful phenotypes, endotypes, and biomarkers that accurately predict the utility of newer, targeted pharmacotherapies is central to advancing asthma management plans tailored to individual patients (Carr and Bleecker 2016; Chung et al. 2018; Zervas et al. 2018).

SEVERE EOSINOPHILIC ASTHMA

Approximately one-half of patients with severe asthma have elevated levels of eosinophils in their airways despite treatment with standard controller and relief medications (e.g., high-dose inhaled and systemic corticosteroids) (Wenzel 2005). As white blood cells with involvement in immuno-modulation, repair, and remodeling, eosinophils are recruited into tissues at sites of infection and acute inflammation via the coordinated actions of cytokines and chemokines, signaling proteins secreted by immune cells (Bafadhel et al. 2017; Mayo Clinic 2018). Together with other white blood cells, eosinophils play a prominent role in T-helper cell-driven type 2 inflammation (Fahy 2015).

Eosinophilic asthma is an evolving, clinically and pathobiologically based subtype of persistently severe asthma that is associated with frequent exacerbations and poor prognosis (Buhl et al. 2017). Its onset usually occurs during adulthood, with men and women affected equally (Wenzel 2012). Eosinophilic asthma is characterized by inflammation and swelling or airflow obstruction from the sinuses to the distal airways; shortness of breath is a common symptom. Atopy in eosinophilic asthma is higher than that observed in the general population but less than that reported in early-onset allergic asthma; levels of immunoglobulin E (IgE), a type of antibody involved in allergic responses, may also be elevated (Wenzel 2012). Airway eosinophilia (also a common feature of an allergic asthma phenotype) is a defining characteristic of this subtype (Lotvall et al. 2011; Wenzel 2012). Elevated numbers of peripheral blood eosinophils and eosinophilic inflammation have been shown to correlate with increasing asthma severity, with lung-infiltrating eosinophils contributing to epithelial cell damage and airway remodeling through release of toxins (Bousquet et al. 1990; Dunican and Fahy 2015; Bafadhel et al. 2017). Having a high eosinophil blood count is a risk factor for future asthmatic exacerbations (Zeiger et al. 2014). As an alternative to more difficult-to-obtain sputum and lung tissue eosinophil counts, blood eosinophil count may serve as an accessible biomarker for identifying patients with severe asthma who may be responsive to newer biologic therapies (Katz et al. 2014; FitzGerald et al. 2017; Yancey et al. 2017).

MANAGEMENT OF SEVERE ASTHMA

Several organizations and medical societies have issued guidelines for assessing, managing, and treating asthma (NHLBI 2007; DHHS 2012; Chung et al. 2014; GINA 2017; GINA 2019a). Asthma guidelines have undergone or are currently undergoing revision to update content regarding heterogeneity and type 2 inflammation, biomarkers, and the use of type 2-targeted therapies in treating severe asthma (National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group 2014; GINA 2019a and 2019b).

The goals of long-term asthma management are to minimize disease burden and poor health outcomes and to improve quality of life through optimization of asthma control (NHLBI 2007). Asthma control is directed toward reducing impairment (due to symptoms or functional limitations) and alleviating risk (i.e., reducing exacerbations and emergency care or hospitalization, slowing decline in lung function, and minimizing medication side effects) (NHLBI 2007; DHHS 2012). For quality asthma care, key clinical activities or care components have been defined:

1) Assessment and monitoring of asthma severity and control;

2) Patient education for self-management;

3) Control of environmental factors (e.g., irritants or inhalant allergens) and comorbid conditions;

4) Selection of medication and delivery devices (NHLBI 2007; DHHS 2012).

Ongoing monitoring of asthma severity and control (#1 above) ensures treatment goals are met and therapy is adjusted according to recommendations provided in the evidence-based guidelines (Wechsler 2009). Educating patients (#2) so that they are able to assess their level of asthma control, monitor for worsening symptoms or peak flow, take medications correctly, and avoid aggravating environmental factors depends in large part on point-of-care interactions with healthcare providers (HCPs) (NHLBI 2007; DHHS 2012). Patient education has been associated with reductions in symptoms, fewer limitations on activities, improvements in quality of life, and improved adherence to medications (NHLBI 2007). Additionally, the development of written, collaborative action plans that outline treatment goals and provide instructions for daily care and emergency situations may inform and empower patients for successful self-management (NHLBI 2007). Adherence to the action plan should be evaluated at each follow-up visit to the HCP.

Besides environmental factors and comorbid conditions (#3), other obstacles to achieving good asthma control include a tendency of patients and HCPs to underestimate symptom severity and of patients to underuse certain prescribed medications (Wechsler et al. 2009). In a structured review of patient-completed surveys, some patients reported discomfort with long-term use of inhaled corticosteroids; moreover, at least 50% of patients indicated they did not adhere to higher-dose regimens of inhaled corticosteroids because of concerns over adverse effects (Holgate et al. 2006).

Asthma medications (#4) may be inhaled or systemically administered (orally or parenterally) (NHLBI 2007). Inhalation therapy using metered-dose (hydrofluoroalkane), dry powder, and soft mist inhalers or nebulizers ensures delivery of drug directly into the lung (Kaplan and Price, 2018). According to GINA guidelines, effective use of inhaler devices and maximal adherence requires HCPs select a device in consultation with the patient, taking into account age, inspiratory ability, and other factors, with training and assessment by the HCP at follow up visits (GINA 2017; Kaplan and Price, 2018).

The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report-3 (EPR-3) recommends a stepwise approach that assesses asthma severity at the outset (intermittent asthma at the Step 1 care level; mild persistent asthma at Step 2; moderate persistent asthma at Step 3 or 4; severe persistent asthma at Step 5 or 6) so that treatment may be initiated using guideline-recommended pharmacotherapies specific to the step care level (NHLBI 2007; DHHS 2012). Once treatment based upon severity is established, the focus shifts to whether asthma control has been optimized or whether adjustments in therapy—stepping up or down—are needed. Depending on the frequency and severity of symptoms, and following a check to see if adherence, inhaler technique, and environmental control measures are adequate, therapy may be stepped up to rapidly suppress airway inflammation and to secure prompt control and stepped down, if possible, when asthma is well controlled (usually for three months) to minimize use or dosages of medications needed for maintaining control. (NHLBI 2007; DHHS 2012).

Referral from primary care providers to specialist care (i.e., allergist/immunologist or pulmonologist) for consultation or co-management is recommended for patients whose asthma remains uncontrolled or difficult to control. Specific reasons for referral include two or more bursts of oral corticosteroids in a single year, an exacerbation requiring hospitalization, a Step 4 care level for asthma control, or a need for treatment with a targeted therapy (NHLBI 2007; Wechsler 2009; GINA 2019). Specialist referrals have been shown to favorably affect disease prognosis and patient health status (Price et al. 2017).

PHARMACOLOGIC TREATMENT OF SEVERE ASTHMA

Pharmacologic treatment of asthma involves the use of agents that provide long-term control of symptoms or short-term relief for acute exacerbations. Control agents include inhaled corticosteroids; bronchodilators such as long acting beta$_2$-agonists, long-acting muscarinic antagonists, and theophylline; leukotriene modifiers; oral corticosteroids; and biologic agents targeted to specific asthma phenotypes (Morris 2019). Quick relief medications include systemic (oral or intravenous) corticosteroids, short-acting beta$_2$-agonists, and short-acting muscarinic antagonists (e.g., ipratropium) (DHHS 2012; Morris 2019).

Corticosteroids, Beta$_2$-Agonists, Leukotriene Modifiers, and Muscarinic Antagonists

For patients with mild, moderate, or severe persistent asthma, inhaled corticosteroids (low-, medium-, or high-dose) are taken daily as the mainstay control therapy, as these agents suppress type 2 inflammation and are the most effective in maintaining long-term control (Fahy 2015; DHHS 2012). However, for some patients, the additional benefit of higher doses may not outweigh the risk of corticosteroid-associated adverse effects (Wechsler 2009).

Systemic corticosteroids are used to treat patients whose severe asthma remains uncontrolled at the Step 6 care level despite the use of high-dose inhaled corticosteroids and long acting beta$_2$-agonists (NHLBI 2007). As an alternative to oral administration, intramuscular depot injections of corticosteroids may be considered for those patients who are at high risk of being non-adherent (NHLBI 2007). Because serious adverse effects—osteoporosis, fractures, diabetes, hypertension, cardiovascular disease, and reduced growth velocity in children—are associated with long term use of oral corticosteroids, short treatment courses are preferred. However, chronic use of oral corticosteroids was shown to occur frequently among patients enrolled in a registry for severe asthma (Heffler et al. 2019). Approximately 40% of patients with severe asthma receive three or more oral corticosteroid prescriptions annually (Bleecker and Castro 2019).

Beta$_2$-agonists (albuterol, salmeterol, formoterol) relax bronchial smooth muscle, reversing bronchospasm in asthmatic airways. Long-acting beta$_2$-agonists may be used as add-on therapy (but never as monotherapy owing to an increase risk of severe exacerbations) for those patients with moderate or severe persistent asthma who require more than inhaled corticosteroids alone to control asthma over the long-term (DHHS 2012, Mayo Clinic 2017). For quick relief of symptoms in intermittent or persistent asthma, inhaled short-acting beta$_2$-agonists are recommended on an

as-needed basis; however, a pattern of increasing use or use of short-acting beta$_2$-agonists for more than 2 days a week is indicative of uncontrolled asthma and a need to step up treatment (DHHS 2012).

Also recommended as add-on oral therapies for mild to moderate persistent asthma are montelukast and zafirlukast, both leukotriene-receptor antagonists, and the 5-lipoxygenase inhibitor zileuton. Indicated for the prophylaxis and chronic treatment of asthma, these agents inhibit the untoward actions of endogenous leukotrienes (principally bronchospasm, increased vascular permeability, mucosal edema, and inflammatory cell infiltration) (Horwitz et al. 1998; Morris 2019).

Tiotropium bromide, a long-acting muscarinic antagonist, promotes bronchodilation and reduces mucus secretion; it may also exert an anti-inflammatory effect (Mansfield and Bernstein 2019). Available for oral inhalation, tiotropium is indicated for long-term, once daily maintenance of asthma in patients 6 years of age and older. Based on positive outcomes observed in randomized clinical trials (RCTs), tiotropium is recommended as add-on therapy to inhaled corticosteroids and long-acting beta$_2$-agonists before stepping up to biologics for patients with severe asthma (GINA 2017; Hamelmann 2018). Tiotropium-associated improvements in lung function and symptom control and reduction in exacerbation risk have been shown to be independent of asthma phenotype (Casale et al. 2018).

Biologic Therapies

Patients whose severe asthma is not adequately controlled with inhaled corticosteroids, bronchodilators, and leukotriene inhibitors or whose asthma is controlled but are at risk of untoward effects from high-dose, long-term corticosteroids may benefit from newer biologic therapies (see Textbox). One biologic agent that effectively neutralizes IgE-mediated responses has been approved for the treatment of allergic asthma, a moderate to severe asthma phenotype characterized by allergic rhinitis, atopy, and elevated levels of IgE. Other biologic therapies that disrupt cellular signaling through interleukin (IL) molecules—glycoproteins produced by white blood cells that are involved in immunomodulation—have been approved for the treatment of moderate and/or severe eosinophilic asthma.

BIOLOGIC AGENTS USED IN THE TREATMENT OF SEVERE UNCONTROLLED ASTHMA

Omalizumab, a monoclonal antibody (mAb) directed against human IgE, is indicated for moderate to severe persistent asthma in patients six years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (DailyMed 2019a). Administered via subcutaneous injection, omalizumab inhibits the binding of IgE to high affinity receptors located on the surface of mast cells and basophils, preventing cellular release of inflammatory mediators (Yancey et al. 2017; Morris 2019). In RCTs that evaluated patients with moderate to severe asthma with an allergic phenotype, treatment with omalizumab was associated with lower exacerbations rates, fewer emergency department visits, and lower inhaled corticosteroid dose than placebo (Holgate et al. 2004; Bousquet et al. 2005; Humbert et al. 2005; Hanania et al. 2011). Omalizumab has been shown to benefit patients with high levels of IgE, blood eosinophils, and periostin, a matricellular protein (Bleecker and Castro 2019).

Mepolizumab is an IL-5 antagonist mAb indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (DailyMed 2019b). IL-5, also known as human eosinophil differentiating factor, is a cytokine produced by T helper 2 cells and type-2 innate lymphoid cells. IL-5 regulates eosinophil maturation, activation, and survival (Campbell et al. 1987; Bafadhel et al. 2017). Administered via subcutaneous injection, mepolizumab inhibits binding of IL-5 to eosinophils. In randomized clinical trials (RCTs), mepolizumab significantly reduced the risk of exacerbations, improved control of asthma symptoms, and improved health-related quality of life in patients with severe eosinophilic asthma compared with placebo, with a significant oral glucocorticoid-sparing effect (Pavord et al. 2012; Bel et al. 2014; Ortega et al. 2014; Chupp et al. 2017). In addition to receiving mepolizumab in a clinic setting, patients will have the option to self-administer mepolizumab at home, once every four weeks, using an auto-injector or a pre-filled safety syringe (Brooks 2019a).

Reslizumab is an IL-5 antagonist mAb indicated for add-on maintenance treatment of patients with severe asthma, aged 18 years and older, with an eosinophilic phenotype (DailyMed 2019c). By binding to circulating IL-5, reslizumab down-regulates the IL-5 signaling pathway, inhibiting blood and tissue eosinophilia (Egan et al. 1999; Bjermer et al. 2016). Reslizumab is administered via intravenous injection. Compared with placebo, reslizumab was shown in RCTs to significantly reduce the frequency of asthma exacerbations, to improve pulmonary function, and to improve quality of life in patients with severe eosinophilic asthma (Castro et al. 2011; Castro et al. 2015; Bjermer et al. 2016; Corren et al. 2016). Treatment with reslizumab was associated with an oral glucocorticoid-sparing effect based on a significant reduction in corticosteroid dose in patients with eosinophilic granulomatosis with polyangiitis, an eosinophilic vasculitis characterized by severe asthma (Kent et al. 2018).

Benralizumab is an afucosylated mAb directed against the interleukin-5 receptor alpha-subunit. By binding to IL-5 receptors on the surface of eosinophils and basophils, benralizumab induces cellular death (Zervas et al. 2017). Administered via subcutaneous injection, benzralizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, with an eosinophilic phenotype (DailyMed 2019d). In RCTs, benralizumab was shown to significantly reduce annual exacerbation rates and to improve total asthma symptom scores compared with placebo in patients with severe uncontrolled asthma with eosinophilia (Bleecker et al. 2016; FitzGerald et al. 2016). An oral glucocorticoid-sparing effect of benralizumab was demonstrated for patients who had severe asthma with persistent eosinophilia despite treatment with inhaled and oral corticosteroids and long-acting beta$_2$-agonists (Nair et al. 2017).

Dupilumab is a mAb directed against the alpha subunit of the interleukin 4 receptor that blocks both IL-4 and IL 13 signal transduction (Zervas et al. 2017). Like IL-5, IL-4 and IL-13 are cytokines secreted by T helper 2 cells and are implicated in the pathophysiology of asthma and atopic diseases (Wenzel et al. 2013). Dupilumab is indicated as an add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma (DailyMed 2019e). Dupilumab is self-administered via subcutaneous injection in the home setting. In one RCT, patients with moderate to severe asthma who received dupilumab had significantly lower rates of exacerbation than patients who received placebo (Wenzel et al. 2013). In another RCT conducted in patients with uncontrolled asthma, treatment with dupilumab was associated with lower exacerbation rates, improved lung function, and better asthma control than treatment with placebo; greater benefits where observed in patients with higher levels of eosinophils at baseline (Castro et al. 2018). Dupilumab treatment reduced oral glucocorticoid use compared with placebo while reducing exacerbation rates and improving lung function (Rabe et al. 2018).

REAL-WORLD EVIDENCE AND SEVERE ASTHMA

Recommendations in treatment guidelines are typically graded according to the strength of the available scientific evidence. RCTs are assigned the highest category of evidence; their findings provide the basis for guideline-recommended medical therapy (Herland et al. 2004). RCTs, which are designed to detect a cause-and-effect relationship between an intervention under investigation and a pre-determined clinical outcome, employ restrictive inclusion criteria to control variability and ensure data quality (Price et al. 2015; Sherman et al. 2016). While RCTs are internally valid, their external validity is limited; that is, their findings may not generalize to patient populations in clinical practice. In one study that included 870 patients with obstructive lung disease from nine general practices and three hospital outpatient clinics, only 5.4% of patients with asthma met selection criteria commonly used in RCTs (Herland et al. 2004).

RWE provides clinical evidence of the actual use and of the benefits or risks of medicines not derived from traditional clinical trials (Corrigan-Curay et al, 2018; FDA 2018, 2019a, 2019b). RWE is generated through the application of research methods from real-world data (RWD), primarily data that describe patient health status or healthcare delivery. RWD are routinely collected from medical billing and claims, patient and provider surveys, registries and other observational cohort studies, electronic devices and social applications, and electronic health records (EHRs) (Sherman et al. 2016; FDA 2019a). RWE has the potential to supplement the findings of RCTs to address clinical challenges (e.g., comorbidities and lifestyle factors) and the resulting gaps in care for significant numbers of patients in everyday practice (Price et al. 2015; Sherman et al. 2016). High quality RWE may inform not only patient care but also medical product development, outcomes research, quality improvement initiatives, safety monitoring, and comparative effectiveness studies (Price et al. 2015; Sherman et al. 2016).

RWE has been used to characterize patients with asthma and to obtain a clearer impression of treatment effects and outcomes outside of more restrictive clinical trial settings. The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens (TENOR) registry (n=4,456 patients) has provided insight into health outcomes and barriers to care for patients with severe or difficult-to-treat asthma (Chipps et al. 2012a and 2012b). Key TENOR observations include high rates of healthcare utilization and substantial clinical burden despite standard-of-care treatment, with uncontrolled asthma and recent exacerbation history predictive of future exacerbations. In a follow-up study that assessed longitudinal data (TENOR II), severe asthma remained a burden more than a decade later, with patients having poorly (58.1%) or very poorly (34.2%) controlled asthma as evidenced by reduced lung function, as well as a high degree of comorbidity (Chipps et al. 2017).

Other real-world, prospective observational studies are currently underway to assess longitudinal progression and outcomes of disease in severe asthmatics (NHLBI, identifier NCT01780142), to employ mechanistic approaches enabling prediction of phenotype stability and pharmacologic responses (NHLBI, identifier NCT01606826), and to establish the epidemiology and medical management (including use of standard therapies and biologics) of adults with severe asthma who are under the care of subspecialists (AstraZeneca, NCT03373045). Real-world observational studies are evaluating the effectiveness, safety, and use of biologic therapies in patients with

allergic asthma (Braunstahl et al. 2013; Casale et al. 2019; MacDonald et al. 2019) and in patients with severe eosinophilic asthma (Zhang et al. 2017; Bjerrum et al. 2018; Chen et al. 2019; Dupin et al 2019; Gelhorn et al. 2019; Hahn et al. 2019; Llanos et al 2019; Ortega et al 2019; Perez de Llano et al. 2019; Sharma et al. 2019).

Real-world pragmatic clinical trials differ from classical RCTs with regard to setting and patient population but may employ similar design elements and use of comparators (Price et al. 2015). Pragmatic trials afford an opportunity to incorporate clinical research into clinical practice (Duke Margolis Center for Health Policy 2017). An example of a pragmatic trial is the Salford Lung Study, which included patients (n=4,275) with symptomatic asthma who were receiving maintenance inhaler therapy (Elkhenini et al. 2015; Woodcock et al. 2017). Results of the open-label, randomized, controlled, two-arm effectiveness trial demonstrated once daily treatment with the corticosteroid fluticasone furoate plus the long-acting $beta_2$-agonist vilanterol improved asthma control when compared with optimized usual care, without increasing the risk of serious adverse events (Woodcock et al. 2017).

RETROSPECTIVE COHORT ANALYSIS

To explore how real-world observations may offer insight into the challenges and opportunities associated with uncontrolled asthma, RWE was generated from de-identified RWD sourced from Practice Fusion a Veradigm™ EHR. As the largest, cloud-based EHR platform of ambulatory patients in the US, Practice Fusion supports efficient patient care and disease management via secure, bi-directional communication between Practice Fusion and HCPs (Veradigm, 2019).

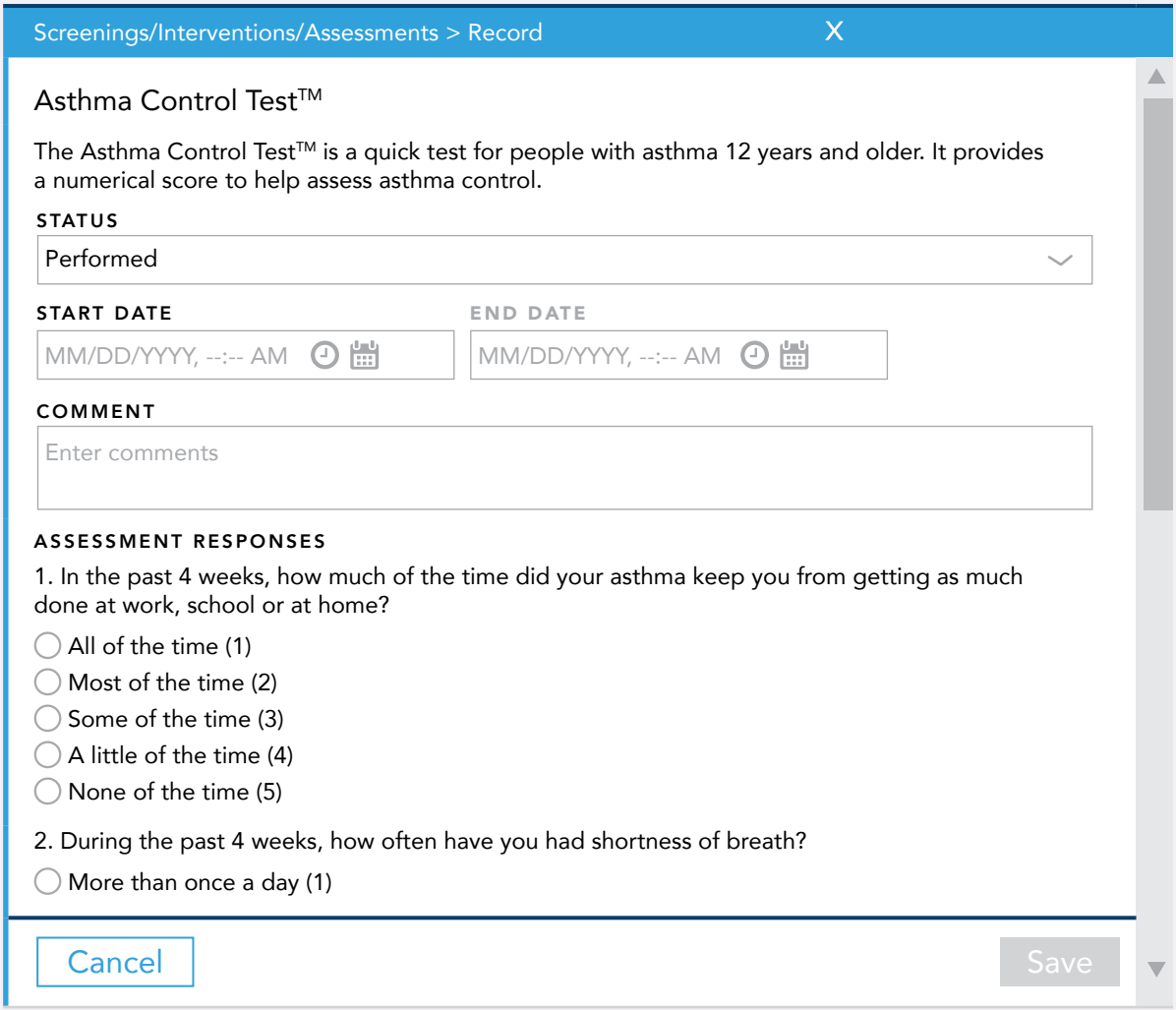
The Asthma Control Test™ is available on the Practice Fusion platform. The ACT is a five question, multi-dimensional health survey that assesses daytime and nighttime asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and patient perception of asthma control during the previous four weeks. The ACT has been shown to be reliable and valid when self-administered by patients or when administered by their HCPs (Nathan et al. 2004; Genco et al. 2018). The ACT appears on the platform as shown in **Figure 1**.

The objectives of this retrospective cohort analysis were to

1) characterize ambulatory patients with a diagnosis of asthma who required additional therapy for control of asthma symptoms; and

2) evaluate the impact of blood eosinophils levels on personalization of asthma care.

FIGURE 1 | **The Asthma Control Test on the Practice Fusion Platform**



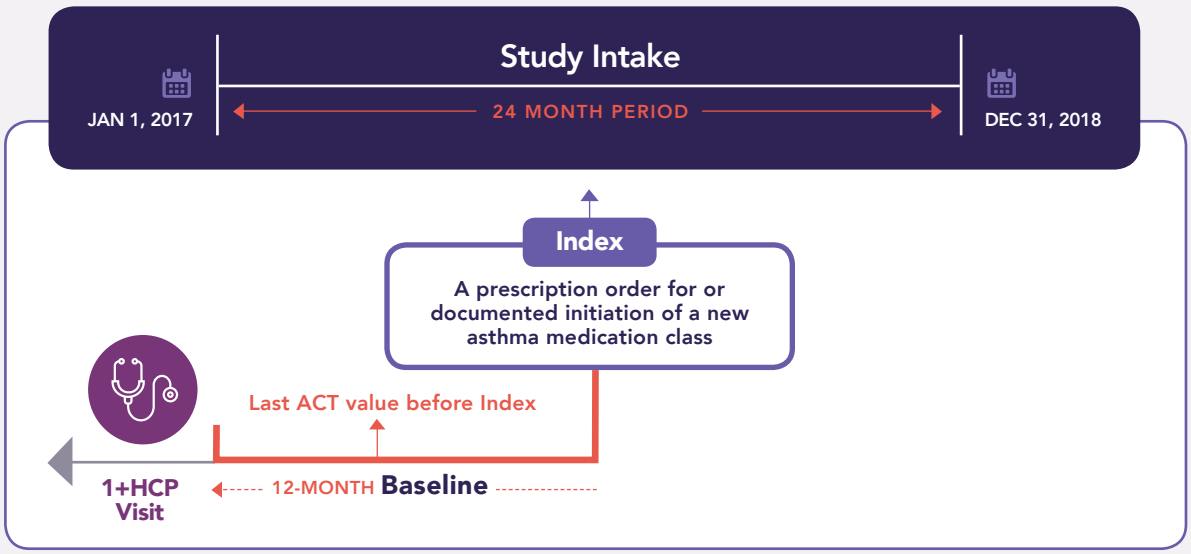
The image above is the first of several screens that a healthcare provider views when administering the ACT. The ACT, a patient-reported outcome measure administered through the Practice Fusion EHR, is used clinically to assess asthma control. Radio buttons allow providers to select patient-reported responses during office visits or phone consults. Results are saved as part of the patient's longitudinal medical record.

Study Design

The study design is shown in **Figure 2**. Inclusion criteria were as follows:

- Have a documented diagnosis of asthma (by ICD-9-CM code or ICD-10-CM code transposed to ICD-9-CM);
- Have a prescription order for or documented initiation of at least one medication from an unused asthma drug class for control of persistent asthma (i.e., not previously recorded in the patient history); new medications had to be added to inhaled corticosteroid (ICS) or to ICS and long-acting beta$_2$-agonist (LABA) treatment during study intake between January 1st, 2017 and December 31st, 2018 (the Index date);
- Be 5 years of age or older at Index;
- Have at least one HCP visit more than 12 months prior to Index;
- Have a blood eosinophil lab result recorded during the 12-month period prior to Index (Baseline).

FIGURE 2 | Study Design



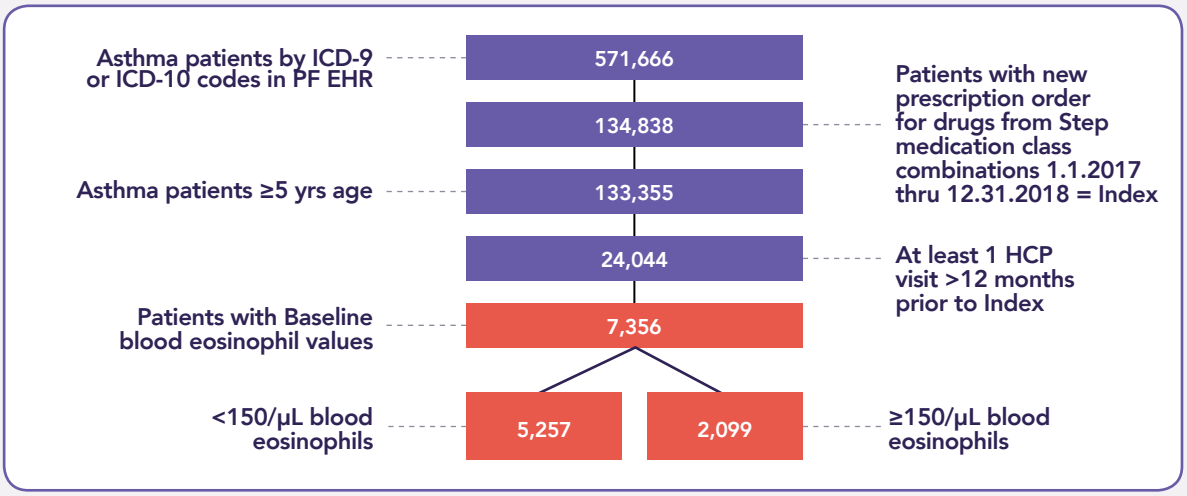
Abbreviations: ACT=asthma control test; HCP=healthcare provider.

Patients were evaluated as a single group (All Patients) and were stratified further according to baseline blood eosinophil counts (<150 cells/μL vs ≥150 cells/μL) and age (Pediatric [≥5-<18 yr] vs Adult [≥18 yr]) into the following four cohorts:

- Pediatric <150 cells/μL;
- Pediatric ≥150 cells/μL;
- Adult <150 cells/μL;
- Adult ≥150 cells/μL.

Because there is no universally accepted threshold for baseline blood eosinophil count as a predictive biomarker in guiding therapeutic choices, 150 cells/μL was used to establish the cohorts based on a study reporting a measurable increase in burden of disease above this cutoff (Tran et al. 2015) and other studies demonstrating efficacy of some biologic therapies at or above this threshold (Bel et al. 2014; Katz et al. 2014; Ortega et al. 2014; Ortega et al. 2015; Ortega et al. 2016; Nair and O'Byrne. 2016; Goldman et al. 2017; Yancey et al. 2017; FitzGerald et al. 2018).

FIGURE 3 | Sample Selection



Abbreviations: ICD-9=International Classification of Disease, Ninth Revision; ICD-10=International Classification of Disease, Tenth Revision; PF EHR=Practice Fusion Electronic Health Record; yrs=years; HCP=healthcare provider; Baseline= 12-month period before Index; μL=microliter.

RESULTS

During study intake (CY 2017 and CY 2018), 134,838 patients were provided a prescription order for or were documented to have initiated a step treatment for control of moderate or severe asthma (**Figure 3**). From this pool, 7,356 patients met additional criteria for age, provider visit, and blood eosinophil count.

Pediatric patients were found to comprise less than 4% of the target population. Given this low percentage, with the exception of patient demographics, vital signs, lab assessments, and provider specialty (**Table 1**), the analyses focused on the all-patient group (pediatric and adult cohorts combined) and the adult (only) cohorts (<150 cells/μL and ≥150 cells/μL).

Patient Characteristics

Baseline demographics, vital signs, blood eosinophil counts, and specialty of providers ordering or documenting the Index medication are shown in **Table 1**. Most analysis-qualified patients were adult (96.6%) and female (65.2%). In the pediatric cohorts, more than one-half of patients were male.

The mean age (SD) for the all-patient group (57.6 [17.9] yr) was greater than that reported in observational cohort studies of pediatric and adult patients with asthma and severe uncontrolled asthma (range, 38.0 [16.6]-52.1 [16.1]) (Zeiger et al. 2017; Suruki et al. 2017) and in a post-hoc analysis of an RCT conducted in patients with severe eosinophilic asthma (range, 46.4 [11.3]-45.5 [9.9]) (Katz et al, 2014). Likewise, mean ages (SD) for the adult cohorts in this analysis (58.9 [16.0] and 60.0 [15.6]) were greater than those reported for adult patient cohorts with persistent asthma in an observational study of patients with severe uncontrolled asthma (44.8 [13.3]-47.4 [12.2]) (Zeiger et al. 2014). Over 80% of patients in the adult cohorts in this analysis were 45 years or older.

Across the cohorts, more patients resided in the Southern US (cohort range, 38.6%-53.5%) than in any other region. Lowest patient densities were localized to the Mid-West (cohort range, 8.1%-13%). More than one-third of patients in each adult cohort had a history of smoking. Across the pediatric and adult cohorts, mean BMI (SD) ranged from 27.6 (7.1) to 31.8 (7.8); for both adult cohorts, the mean BMI exceeded the threshold for Class 1 obesity (BMI >30). More than 25% of all patients had blood eosinophil counts ≥150 cells/μL at baseline. In the adult cohort with baseline eosinophil counts ≥150 cells/μL, 995 patients (49.3%) had counts ≥300 cells/μL.

Most (>90%) patients in the adult cohorts had prescription orders from or were documented to have initiated a new class of control pharmacotherapy by a primary care specialist at Index. Pediatricians and primary care providers ordered or documented Index medications for most pediatric patients. Pulmonologists and allergists/immunologists ordered or documented Index medications for fewer than 3% of all patients.

TABLE 1 | **Patient Demographics, Vital Signs, and Provider Specialty**

VARIABLE, N (% OF COHORT) UNLESS OTHERWISE INDICATED	Patients with Asthma				
	All Patients* N=7,356	Pediatric <150/µL N=172	Pediatric ≥150/µL N=80	Adult <150/µL N=5,085	Adult ≥150/µL N=2,019
Patients, n (% of all)	7,356 (100)	172 (2.3)	80 (1.1)	5,085 (69.1)	2,019 (27.4)
GENDER					
Female	4,796 (65.2)	84 (48.8)	36 (45.0)	3,384 (66.5)	1,292 (64.0)
Male	2,552 (34.7)	88 (51.2)	44 (55)	1,694 (33.3)	726 (36.0)
Not recorded	8 (<1.0)	0 (0.0)	0 (0.0)	7 (<1.0)	1 (<1.0)
AGE					
Age, mean yr (SD)	57.6 (17.9)	11.7 (3.7)	10.6 (3.8)	58.9 (16.0)	60.0 (15.6)
5-11 yr	125 (1.7)	80 (46.5)	45 (56.3)	0 (0.0)	0 (0.0)
12-17 yr	127 (1.7)	92 (53.5)	35 (43.8)	0 (0.0)	0 (0.0)
18-44 yr	1,304 (17.7)	0 (0.0)	0 (0.0)	970 (19.1)	334 (16.5)
45-64 yr	2,863 (38.9)	0 (0.0)	0 (0.0)	2,048 (40.3)	815 (40.4)
≥65 yr	2,937 (39.9)	0 (0.0)	0 (0.0)	2,067 (40.6)	870 (43.1)
RACE					
White	3,145 (42.8)	43 (25.0)	25 (31.3)	2,168 (42.6)	909 (45.0)
Black	752 (10.2)	23 (13.4)	9 (11.3)	559 (11.0)	161 (8.0)
Other	555 (7.5)	14 (8.1)	11 (13.8)	379 (7.5)	151 (7.5)
Not recorded	2,904 (39.5)	92 (53.5)	35 (43.8)	1,979 (38.9)	798 (39.5)
ETHNICITY					
Hispanic/Latino	1,050 (14.3)	45 (26.2)	27 (33.8)	689 (13.5)	289 (14.3)
Not Hispanic/Latino	6,306 (85.7)	127 (73.8)	53 (66.3)	4,396 (86.5)	1,730 (85.7)
GEOGRAPHY					
Northeast	1,800 (24.5)	27 (15.7)	14 (17.5)	1,238 (24.3)	521 (25.8)
Midwest	807 (11.0)	14 (8.1)	8 (10.0)	523 (10.3)	262 (13.0)
South	3,233 (44.0)	92 (53.5)	41 (51.3)	2,320 (45.6)	780 (38.6)
West	1,508 (20.5)	39 (22.7)	17 (21.3)	998 (19.6)	454 (22.5)
Not recorded	8 (<1.0)	0 (0.0)	0 (0.0)	6 (<1.0)	2 (<1.0)

continued on next page

TABLE 1 | **Patient Demographics, Vital Signs, and Provider Specialty** *Continued*

VARIABLE, N (% OF COHORT) UNLESS OTHERWISE INDICATED	Patients with Asthma				
	All Patients* N=7,356	Pediatric <150/µL N=172	Pediatric ≥150/µL N=80	Adult <150/µL N=5,085	Adult ≥150/µL N=2,019
INSURANCE					
Commercial/Other	2,819 (76.9)	87 (88.8)	39 (92.9)	1,917 (76.4)	776 (76.2)
Medicare	1,063 (29.0)	0 (0.0)	0 (0.0)	749 (29.9)	314 (30.8)
Medicaid	532 (14.5)	23 (23.5)	9 (21.4)	351 (14.0)	149 (14.6)
Not determined	3,690 (50.2)	74 (43.0)	38 (47.5)	2,577 (50.7)	1,001 (49.6)
No Insurance	34 (<1.0)	0 (0.0)	1 (2.4)	25 (1.0)	8 (<1.0)
SMOKING					
History of Smoking	2,626 (35.7)	1 (<1.0)	1 (1.3)	1,893 (37.2)	731 (36.2)
VITAL SIGNS					
Weight	6,821 (92.7)	28 (16.3)	9 (11.3)	4,847 (95.3)	1,937 (95.9)
Weight, mean (SD)	186.8 (50.7)	160.9 (40.6)	171.7 (76.0)	185.9 (50.6)	189.3 (50.8)
BMI	6,821 (92.7)	28 (16.3)	9 (11.3)	4,847 (95.3)	1,937 (95.9)
BMI, mean (SD)	31.4 (7.8)	27.6 (7.1)	29.7 (13.3)	31.2 (7.8)	31.8 (7.8)
BLOOD EOSINOPHILS					
≥300/µL	1,049 (14.3)	0 (0.0)	54 (67.5)	0 (0.0)	995 (49.3)
≥150/µL-299/µL	1,050 (14.3)	0 (0.0)	26 (32.5)	0 (0.0)	1,024 (50.7)
<150/µL	5,257 (71.5)	172 (100)	0 (0.0)	5085 (100)	0 (0.0)
PROVIDER SPECIALTY PRECRIBING/DOCUMENTING INDEX MEDICATION CLASS					
Allergists/Immunologists	35 (<1.0)	2 (1.2)	2 (2.5)	21 (<1.0)	10 (<1.0)
Primary Care	6,581 (89.5)	76 (44.2)	16 (20.0)	4,648 (91.4)	1,841 (91.2)
Pediatrics	177 (2.4)	92 (53.5)	61 (76.3)	17 (<1.0)	7 (<1.0)
Pulmonology	159 (2.2)	1 (<1.0)	0 (0.0)	114 (2.2)	44 (2.2)
Other	200 (2.7)	0 (0.0)	1 (1.3)	144 (2.8)	55 (2.7)
Not recorded	204 (2.8)	1 (<1.0)	0 (0.0)	141 (2.8)	62 (3.1)

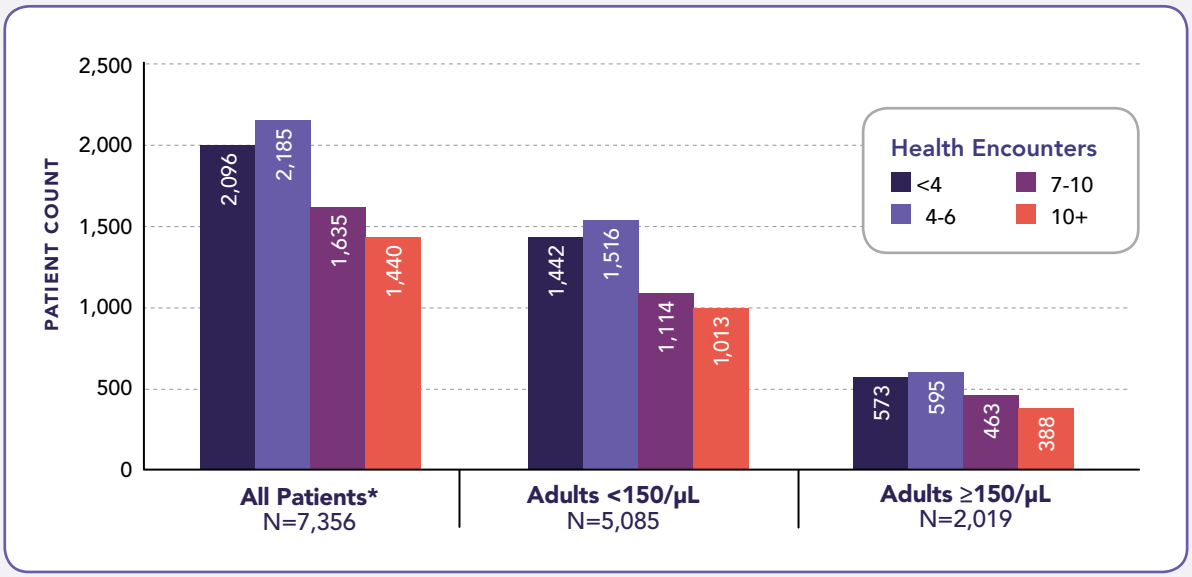
*Includes pediatric and adult patients with baseline blood eosinophil counts.

Abbreviations: µL=microliter; SD=standard deviation; BMI=body mass index.

Healthcare Utilization

For patients with more than one visit to an HCP before Index, the mean (SD) number of healthcare encounters (e.g., office visits, phone consultations, and laboratory assessments) during Baseline was 7.4 (7.0) (**Figure 4**). Approximately 42% of patients in both adult cohorts had 7 or more healthcare encounters during the one-year Baseline period, similar to the reported frequency of annual office visits for patients with moderate or severe persistent asthma (Antonicelli et al. 2004). The percentage of patients with <4, 4-7, 7-10, or 10+ healthcare encounters was similar between the adult cohorts, a finding that may not align with observations of greater healthcare utilization associated with increased blood eosinophil levels in persistent asthma (Tran et al. 2015).

FIGURE 4 | **Healthcare Utilization Summary at Baseline**



*Includes pediatric and adult patients with baseline blood eosinophil counts.

Any documented healthcare encounter (e.g., office visit, phone consult, lab assessment) is reported as all-cause healthcare utilization during each patient's one year Baseline period before Index.

Comorbidities

Burden of disease was evaluated using the Charlson Comorbidity Index (CCI) (Charlson et al. 1987). The CCI, which predicts the one-year mortality for patients with a range of comorbid conditions, has been used to obtain prognostic outcomes for patients with asthma and coexisting disorders (El Ferkh et al. 2016). Higher global comorbidity (CCI ≥2) has been associated with more time in a severe asthma state or increased risk of mortality (Chen et al. 2016). In the present analysis, comorbidities were recorded at any time in the medical record history of analysis-eligible patients.

A summary of CCI results are shown in **Table 2**. The overall mean (SD) CCI of 1.9 (1.8) for the all-patient group was greater than that reported previously for patients with severe uncontrolled asthma (Zeiger et al. 2014; Zeiger et al. 2017). In the adult cohorts, 43.1% and 45.0% of patients had CCI scores of 2 or more; nearly one-quarter of all patients had CCI scores of 3 or more. Approximately one-third, one-quarter, and one-tenth of patients in the adult cohorts were overweight or obese, had a diagnosis of hypertension, or had a diagnosis of depression, respectively.

TABLE 2 | Comorbidity Summary

VARIABLE, N (% OF COHORT) UNLESS OTHERWISE INDICATED	Patients with Asthma		
	All Patients* N=7,356	Adult <150/µL N=5,085	Adult ≥150/µL N=2,019
Charlson Comorbidity Index, mean (SD)	1.9 (1.8)	1.9 (1.7)	2.0 (1.8)
CCI Group: 0	637 (8.7)	436 (8.6)	157 (7.8)
CCI Group: 1	3,617 (49.2)	2,460 (48.4)	954 (47.3)
CCI Group: 2	1,336 (18.2)	925 (18.2)	407 (20.2)
CCI Group: 3+	1,766 (24.0)	1,264 (24.9)	501 (24.8)
Depression	761 (10.3)	541 (10.6)	219 (10.8)
Hypertension	1,903 (25.9)	1,350 (26.5)	552 (27.3)
Overweight/Obese	2,434 (33.1)	1,675 (32.9)	680 (33.7)

*Includes pediatric and adult patients with baseline blood eosinophil counts.

Comorbidities were recorded at any time in a patient's history before Index.

Abbreviations: µL=microliter; SD=standard deviation; CCI=Charlson Comorbidity Index.

Asthma Control Test

A convenience sample of analysis-eligible patients were documented to have completed the ACT at Baseline (**Table 3**), consistent with frequency of use for other validated assessments available in Practice Fusion. For adults stratified by age (<65 yr and ≥65 yr), mean (SD) ACT scores during baseline were 19.1 (4.7) and 18.6 (5.5), respectively, with corresponding medians (interquartile range [IQR]) of 20 (16, 24) and 20 (15, 23). For individual patients, an ACT score of 19 or less suggests asthma may not be well-controlled and is consistent with a recommendation to step up treatment to attain greater asthma control (DHHS 2012; Chung et al. 2014).

TABLE 3 | Asthma Control Test

ACT SCORES, MEAN (SD) UNLESS OTHERWISE INDICATED	Patients with Asthma		
	All Patients* N=7,356	**18-64 yr** N=4,167	**≥65 yr** N=2,937
Completed, n (% of cohort)	293 (4.0)	172 (4.1)	106 (3.6)
In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school, or at home?	3.9 (1.1)	4.0 (1.0)	3.8 (1.1)
During the past 4 weeks, how often have you had shortness of breath?	3.8 (1.2)	3.8 (1.2)	3.7 (1.3)
During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)
During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?	3.7 (1.3)	3.7 (1.3)	3.7 (1.3)
How would you rate your asthma control during the past 4 weeks?	3.7 (1.1)	3.7 (1.0)	3.6 (1.2)
Total Score	18.9 (5.1)	19.1 (4.9)	18.6 (5.5)

*Fifteen pediatric (≥12-17 yr at Index) and 278 adult (≥18 yr at Index) patients completed the ACT at Baseline.

For patients ≥12 yr of age, each question of the ACT is self-scored on a 5-point scale for symptoms and activities or asthma control rating. Total scores (the sum of the responses obtained for each item) range from 5 (poor asthma control) to 25 (complete asthma control). A total score ≤19 indicates asthma may not be well controlled.

Abbreviations: ACT=asthma control test; SD=standard deviation; yr=year.

Baseline Medications

The percentage of patients with prescription orders for or documentation of control medications was highest for combination ICS/LABA inhalers (89.5%) followed by ICS (80.0%) and long-acting muscarinic antagonists (LAMA) (43.8%) (**Table 4**). ICS use was twice that of LABA use (80.0% vs 39.1%). Percentages of patients with prescriptions or documented use of biologic agents

(omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) or a methylxanthine were low (<1% in each cohort). No patients had prescriptions for or documented use of a 5-lipoxygenase inhibitor (5-LPOi).

The percentage of patients with prescription orders for or documentation of relief medication was highest for short-acting beta$_2$-agonist (SABA) (63%) followed by oral corticosteroids (OCS) and systemic corticosteroids (44.3% and 32.7%, respectively). Patient percentages for a short-acting muscarinic antagonist (SAMA) or methylxanthine were low.

The percentages of patients using ICS/LABA, ICS, and OCS in this analysis were consistent with those shown in observational studies of severe asthma (Zeiger et al. 2017; Heffler et al. 2019) but were generally higher than that shown in an earlier observational study (Antonicelli et al. 2004).

TABLE 4 | Baseline Prescription Medications for Asthma Symptom Control and Relief

MEDICATION SUMMARY, N (% OF COHORT)	Patients with Asthma		
	All Patients* n=7,356	Adult <150/µL n=5,085	≥150/µL n=2,019
Inhaled corticosteroids (budesonide, beclomethasone, ciclesonide, flunisolide, fluticasone, mometasone, triamcinolone)	5,887 (80.0)	4,079 (80.2)	1,597 (79.1)
Oral corticosteroids (methylprednisolone, prednisolone, prednisone)	3,256 (44.3)	2,261 (44.5)	888 (44.0)
Systemic corticosteroids	2,404 (32.7)	1,651 (32.5)	658 (32.6)
Leukotriene receptor antagonist (montelukast)	2,394 (32.5)	1,598 (31.4)	624 (30.9)
Long acting beta agonists (albuterol tablet, formoterol, salmeterol)	2,878 (39.1)	2,023 (39.8)	823 (40.8)
Combination ICS/LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol, fluticasone/vilanterol)	6,584 (89.5)	4,607 (90.6)	1,856 (91.9)
Long acting muscarinic antagonists (tiotropium)	3,225 (43.8)	2,309 (45.4)	896 (44.4)
5-Lipoxygenase inhibitor (zileuton)	0 (0)	0 (0)	0 (0)
IgE monoclonal antibody (omalizumab)	14 (<1.0)	7 (<1.0)	6 (<1.0)
IL-4/IL-13 monoclonal antibody (dupilumab)	6 (<1.0)	3 (<1.0)	3 (<1.0)
IL-5 monocloncal antibodies (benralizumab, mepolizumab, reslizumab)	12 (<1.0)	8 (<1.0)	3 (<1.0)
Methylxanthines (theophylline)	28 (<1.0)	20 (<1.0)	8 (<1.0)
Short acting beta agonist (albuterol, levalbuteral, pirbuterol)	4,682 (63.6)	3,181 (62.6)	1,284 (63.6)
Short acting muscarinic antagonists (ipratropium)	205 (2.8)	134 (2.6)	68 (3.4)

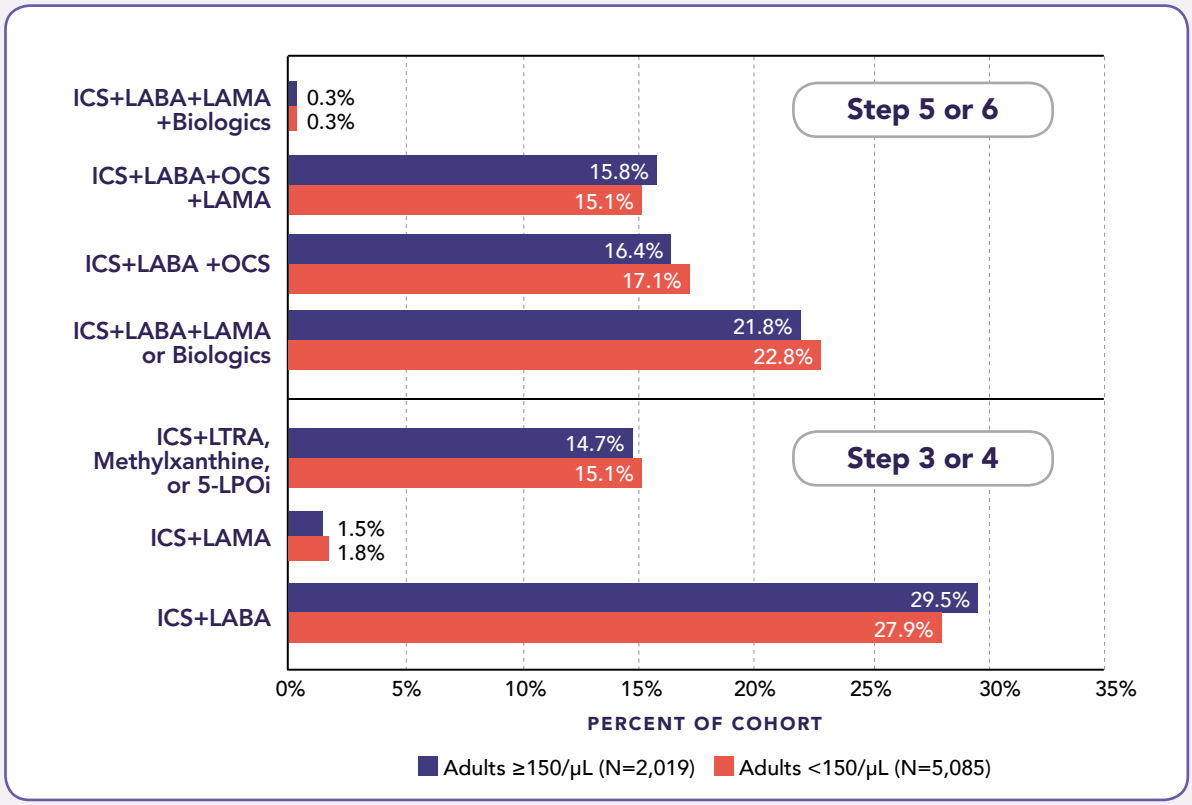
*Includes pediatric and adult patients with baseline blood eosinophil counts.

Abbreviations: µL=microliter; ICS=inhaled corticosteroids; LABA=long-acting beta2-agonists; IgE=immunoglobulin E; IL-4/IL-13=interleukin-4/interleukin 13; IL-5=interleukin-5.

Index Medications

At Index, more than one-half (53.7%) of all patients had new prescription orders for or were documented to have stepped up therapy in a manner consistent with NAEPP or GINA recommendations for severe persistent asthma (Step 5-6); the remaining patients (46.3%) had prescription orders or documentation consistent with recommendations for moderate persistent asthma (Step 3-4) (DHHS 2018, GINA 2018). In the moderate persistent category, more patients (28.2%) stepped up with LABA added to established ICS therapy than with any other recommended add-on therapy (**Figure 5**). In the severe persistent category, more patients (21.9%) stepped up with either a LAMA or a biologic added to established ICS plus LABA therapy than with any other recommended add-on therapy (biologics <1.0%). Patients infrequently stepped up with LAMA added to established ICS therapy for moderate persistent asthma (<2.0%) or with OCS plus a biologic added to established ICS plus LABA therapy (<1%). The distribution was similar between the eosinophil count cohorts.

FIGURE 5 | Index Prescription Medications for Asthma Symptom Control



For Steps 3 or 4, a new class of asthma control treatment was added to or replaced existing medication regimen(s) at Index; options included LABA, LAMA, LTRA, methylxanthine, or 5-LPOi added to ICS. If a patient was indexed on, e.g., LABA with ICS+OCS recorded at baseline, then the patient was included in the ICS+LABA group assuming baseline OCS was for exacerbation. For Steps 5 or 6, a new class of asthma control treatment was added to or replaced existing medication regimens at Index; options included LAMA or Biologics, OCS, OCS and LAMA, or OCS and Biologics added to ICS+LABA.

Abbreviations: ICS=inhaled corticosteroids; LABA=long-acting beta2-agonists; LAMA=long-acting muscarinic antagonists; LTRA=leukotriene receptor antagonist; 5-LPOi=5-lipoxygenase inhibitor; Biologics=monoclonal antibodies against immunoglobulin E, interleukin-4/interleukin-13, or interleukin-5, or interleukin-5 receptor. OCS=oral corticosteroid.

DISCUSSION

Specific goals of long-term asthma management include minimizing disease burden and improving quality of life through optimization of asthma control. Asthma control is directed toward reducing impairment arising from symptoms or functional limitations and alleviating risk caused by exacerbations and hospitalizations, declines in lung function, and medication side effects. For many patients, asthma is well managed with corticosteroids and other medications recommended as part of stepwise therapy. For other patients, severe asthma remains uncontrolled or is only partially controlled with standard medications. To further complicate treatment, the benefits of high-dose corticosteroids may not outweigh the risks of serious untoward effects. These patients may be better served by a biomarker-based approach that facilitates accurate diagnosis and effective use of standard and targeted therapies.

The retrospective cohort analysis provides an example of how RWE may be derived from de-identified ambulatory patient data sourced from Practice Fusion a Veradigm™ EHR. Patient selection was based in part on ICD-9-CM or transposed ICD-10-CM codes encompassing a diagnosis of asthma and evidence of uncontrolled moderate to severe asthma. Blood eosinophil counts for stratification were captured as logical observation identifier names and codes in structured fields and unstructured laboratory result descriptions. The level of supplementation using natural language processing (NLP) was 5.5%. Approximately 2,000 patients had baseline blood eosinophil counts ≥150 cells/μL, a threshold associated with increased healthcare utilization and disease burden, with one half of these patients having counts ≥300 cells/μL. Blood eosinophil counts ≥300 cells/μL may afford HCPs and their patients the flexibility to begin biologic treatment immediately, if appropriate, as part of shared decision-making (Yancey et al., 2017). Despite these findings, prescription orders or documented use of biologics at Baseline and Index across the cohorts were low (both <1%). These findings suggest there is room for consideration of biologics for patients in whom eosinophils may play a pathobiologic role.

Approximately one-third of patients in the analysis were observed to be overweight or obese, with the mean BMI in both adult cohorts greater than the threshold for obesity Class 1 (BMI >30). Hypertension and obesity have been identified in cluster analyses as common comorbidities in later onset adult asthma (ACCP 2018), and weight gain has been associated with long-term use of systemic corticosteroids (Stanbury and Graham 1998). An obesity phenotype in severe asthma has been recognized; weight loss may improve asthma control, lung function, and inflammation (Zervas et al. 2018). In the analysis, CCI global comorbidity indicated increased odds for long-term asthma severity and increased risk of mortality for more than 40% of patients in each of the adult cohorts.

Across the cohorts, mean ACT scores of 19 or less suggested that asthma was not well controlled for a substantial proportion of patients completing the test. The ACT has been designated as a core measure for NIH initiated clinical research given its extensive clinical validation by specialist assessment and spirometry, a minimal clinically important difference of 3 points, low patient burden and risk, and the importance of asthma control as a guideline-stated therapeutic goal (Nathan et al. 2004; Schatz et al. 2009; Cloutier et al. 2012; Alzahrani and Becker 2016). In addition to their use in clinical research settings, patient-reported outcome measures such as the ACT may

be administered by HCPs at the point of care to help track whether an intervention is associated with improvement in a patient's health status or if a change in therapy is required (a reduction in exacerbations may take a year or more to emerge [Buhl et al. 2017]). Patient-reported outcome measures may also be used to evaluate the effectiveness and value of interventions and services at a systems level for creating a quality-oriented healthcare culture (Wagle 2017).

Treatment guidelines recommend referral to respiratory specialists for patients with uncontrolled asthma who reach a Step 4 (moderate) care level; such referrals have a significant impact on disease prognosis and patient health status (NHLBI 2007; GINA 2019; Price et al. 2017). In the present analysis, primary care physicians ordered or documented new medications for over 90% of adult patients, with allergists or pulmonologists ordering or documenting new therapies for fewer than 3% of patients. In a recent survey of 763 clinicians conducted by a medical information website in collaboration with the American College of Chest Physicians, respondents ranked inhaled corticosteroids with long-acting bronchodilators highly; their status as favored medications for patients with moderate to severe asthma is in keeping with guideline recommendations. While clinicians had a favorable impression of biologics, when broken out by subspecialty, only 16% of primary care physicians, 7% of pediatricians, and 2% of emergency medicine physicians indicated they were comfortable prescribing biologic agents compared with 91% of allergists/immunologists and 59% of pulmonologists (Brooks 2019b). Given the oral glucocorticoid-sparing effects reported for biologics, referral to a respiratory specialist may offer opportunity for targeted biologic therapy, as appropriate, and for stepping down corticosteroid exposure, as recommended, to reduce the risk of side effects (Price et al. 2017).

EHR platforms such as Practice Fusion that communicate bi-directionally with HCPs are widely-adopted digital systems that securely manage comprehensive patient health information. Such EHR systems assist in coordinating care across authorized providers by collecting and integrating patient data into the clinical workflow; they provide access to evidence-based tools that support more informed clinical decision-making (HealthIT.gov 2019b). Through linkage with web-based or mobile portals, EHRs may enable communication between HCPs and patients outside of office-based healthcare encounters. Such communication offers opportunities to closely monitor and assess health status and further encourages shared decision-making between HCPs and their patients.

Interactive EHR platforms have the potential to support patients with asthma in a variety of situations. As an example, EHRs may provide HCPs access to outcome measures like the ACT that are used to assess a patient's asthma control and facilitate opportunities for guideline-recommended stepwise adjustment of pharmacotherapy. A low ACT score or 3 point decrement may initiate support to the HCP to consider ordering a white blood cell differential, which may reveal elevated eosinophil counts and a possible need for targeted therapy. In the present analysis, nearly 70% of patients who otherwise qualified had no baseline record of eosinophil counts.

A critical component of patient self-management is a personalized asthma action plan. Patients with action plans that outline treatment goals and provide instruction for daily care and emergency situations have better adherence to treatment regimens, have reduced acute care visits, and are more satisfied overall compared with asthma patients without action plans (Kuhn et al. 2015). EHR algorithms that match evidence-based guidelines to individual patient needs may facilitate completion of plans that HCPs consider with patients and their families. In studies involving

ambulatory care sites, the use of EHRs with these features has been shown to enable delivery of action plans and to result in better asthma quality of care (i.e., increased assessment of asthma control in adults [Gupta et al. 2019] and reductions in exacerbations and lower odds of requiring oral corticosteroids in children [Kuhn et al. 2015]). Additionally, EHR support tools may provide access to educational content, which HCPs may review and consider offering digitally to patients and their designated caregivers through provider-patient portals. Stage specific educational materials available through EHR-linked portals may enhance shared decision-making between patients and their HCPs and empower patients for self-care (Apter 2014; Fiks et al. 2015; HealthIT.gov 2019a).

EHRs have been shown to assist in HCP compliance with evidence-based guidelines. In a program implemented at a hospital affiliated with a regional pediatric healthcare network, patients admitted for exacerbations had reduced inpatient stays and lower risk of 30-day readmissions when the institutional EHR provided HCPs care guidelines hyperlinked to order sets. Hyperlinking and hard stop reminders ensured action plans were completed and provided to patients before discharge. Between 2010 and 2016, use of inpatient asthma care guideline increased 12% (Feaster et al. 2016). Similar strategies may be applied in ambulatory care settings facilitated by support algorithms embedded in EHRs (Kuhn et al. 2015; Bell et al. 2016).

Evidentiary gaps related to real-world safety, effectiveness, and use of medical products have prompted the FDA and industry stakeholders to consider how to leverage RWD from EHRs and other sources for RWE generation to inform best practices for regulatory decision-making and timely and cost-effective drug and biologic development. To evaluate supplemental applications and guide its RWE Program, the FDA will consider whether sources of RWD are fit for use (i.e., reliable and relevant), whether study conduct meets FDA regulatory requirements for monitoring and data collection, and whether various study designs and analytical methods used to generate RWE from RWD may answer regulatory questions (FDA 2019a). The RWE Program will develop guidance for designing clinical trials that include pragmatic design elements and that generate evidence of comparative effectiveness for regulatory decisions (FDA 2019a).

CONCLUSION

EHRs have the potential to provide clinical support and to inform and enable efficient and cost-effective drug and biologic development. The identification of clinically meaningful phenotypes, endotypes, and biomarkers that accurately predict the utility of newer, targeted pharmacotherapies is central to advancing asthma management plans tailored to individual patients. Studies that leverage RWD and RWE from electronic health platforms may provide insight into eosinophilic asthma, other subtypes of severe asthma, and treatment effectiveness in support of such care plans.

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