A novel computerized phenotype-oriented algorithm for asthma diagnostics

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Personal Section

I'd never realized how pivotal the summer of 2016 was in my preparation for Regeneron STS. That summer, I joined the Rutgers Institute for Translational Medicine & Science, a pioneering lab investigating respiratory diseases, primarily asthma. I developed a project with my mentor that focused on the human rhinovirus and took part in various asthma-related pharmacological studies. At the time, I also began to self-study computer science. From Codecademy to ProjectEuler, I spent numerous hours grappling with brand-new concepts in CS and mathematics. Progress was slow at first but I managed to cover the APCS curriculum and beyond by the end of the summer.

In May of 2017, as I was already beginning to plan a new project on the rhinovirus, I was shocked to find out that I couldn't return to the lab for the summer. Worse yet, it was already too late to find positions in other labs: none of the researchers I had contacted responded affirmatively to my requests. The only remaining option was to take on an *in silico* project without a mentor.

My background in asthma pathophysiology and computer science from the previous year allowed me to study trends in asthmatics and improve upon current practices. After studying the well-established EPR-3 and GINA report guidelines, I noticed a major shortcoming in the categorization of asthma severity in the clinical setting. Although assessment of impairment factors usually leads to successful disease management in majority of asthmatics, the cases of discordant and difficult-to-treat asthma demand the accurate phenotyping of patients based on risk factors to determine targeted therapy. The lack of objective parameters in defining each risk factor leads to inefficiency, subjectivity, and therefore, variation among clinicians' or subspecialists' decision-making. The next step was to analyze trends in risk factors via systematic review and subsequently, meta-synthesis, to establish objective parameters for asthma diagnostics and design a phenotype-oriented algorithm. At this point, I researched recent advances in computerized clinical decision support systems and found that, despite their varying degrees of success, the systems were generally not well integrated into clinicians' and subspecialists' workflow. This finding led to my next step: computerized implementation and comparison of the EPR-3-, GINA report-, and meta-synthesis-based algorithms to elucidate the advantages of the novel algorithm.

I had gained practical experience in a pioneering lab and learned about the intricacies of literature review and quantitative data analysis from my mentor the previous year. However, through my recent project, I became involved in not only the research side, but also the clinical aspect of disease diagnostics. I was able to immerse myself in the systematic review and meta-synthesis as well as development of source code to implement algorithms. In my self-driven endeavor to design the phenotype-oriented algorithm, I independently explored the processes of systematic review and meta-synthesis to collect and compile data of various outcome measures. The interdisciplinary approach to problem-solving inspired me to broaden my horizons to apply such an approach to any scientific challenge I encounter in the future.

To younger scientists: Even if conducting research means designing a project from your bedroom, the struggle is worthwhile regardless of the end result.

Abstract

Physicians in the US currently rely on two guidelines for asthma diagnostics: the EPR-3 and the GINA report. Due to the ten year difference in publication time, a comparison between both guidelines is necessary. Additionally, while the guidelines include defined parameters for impairment factors, patient-specific risk factors remain unparameterized. By parameterizing the risk factors and following a phenotype-oriented diagnostic approach, clinicians may be may be able to improve asthma diagnostics with respect to speed and accuracy consistency. Computerized algorithms for the EPR-3 and GINA report were coded in Java and compared with respect to therapy recommendations for mild, moderate, and severe asthmatics. A systematic literature review and meta-synthesis was performed in the PubMed database to determine parameters for asthma phenotype categorization. A computerized algorithm was coded based on determined parameters. and compared to the EPR-3- and GINA report-based algorithms with respect to therapy recommendation for asthmatics of five established phenotypes. The GINA report's recommendation of specialist assessment for severe asthma supported the emphasis on asthma as a heterogeneous disease since publication of the EPR-3. The systematic-review-based algorithm recommended targeted therapy such as anti-IL-5 for the late-onset eosinophilic phenotype when compared to the EPR-3 and GINA algorithms' recommended inhaled corticosteroids with long-acting ß-agonist, suggesting the potential of the phenotype-oriented approach for personalizing clinical decisions. The systematic review-based algorithm may become part of clinical decision support systems to reduce variability of asthma diagnostics in the near future. Through further investigation, the approach to parameterize factors may be applicable to diagnostics for other heterogeneous diseases such as cancer.

Introduction

Asthma is the most prevalent chronic respiratory disease in the US, affecting ~24.6 million individuals nationwide (National Center for Health Statistics, 2015). Additionally, asthma poses a significant financial burden, costing the US over $56 billion in medical costs and missed school/work days in 2007 (Centers for Disease Control and Prevention, 2011). It has been previously demonstrated that poor control and exacerbations are major contributors to medical costs (Bahadori et al., 2009; Doz et al., 2013). For instance, Sullivan et al. (2017) found a strong association between poor control/exacerbations and higher medical expenses. Effective control, therefore, is a priority in proper asthma management.

Current asthma guidelines

Currently, physicians utilize two official asthma diagnosis and management guidelines to assist in clinical decision-making: the Expert Panel Report 3 (EPR-3; National Heart, Lung, and Blood Institute, National Institutes of Health, 2007) and the annual Global Initiative for Asthma (GINA) report (Global Initiative for Asthma, 2017). Although the GINA 2017 report contains the most recently updated guidelines, the decade-old EPR-3 continues to affect the clinical decisions of many physicians. A comparison between the two guidelines with respect to asthma severity/control categorization is therefore necessary.

Table. 1. Asthma severity/control assessment includes both impairment and risk factors. SABA=Short-acting ß-agonist, FeNO=Fractional exhaled nitric oxide, IgE=Immunoglobulin E.

Impairment factors	Risk factors
Symptom frequency	Severe exacerbation frequency
Nighttime awakenings	Presence of comorbidities
SABA use frequency	Allergic status
Interference with normal activity	Eosinophil count
Lung function	Neutrophil count
	Leukotriene level
	FeNO level
	IgE level
	Drug responsiveness
	Genetic predisposition

The EPR-3 and GINA report feature parameterized bounds for impairment factors of asthma but only qualitatively outline risk factors (Table 1; Table 2; Global Initiative for Asthma, 2017; Lockey, 2014; National Heart, Lung, and Blood Institute, National Institutes of Health, 2007). While impairment factors are well-established factors in asthma severity/control assessment, the cases of discordant and difficult-to-treat asthma present obstacles to effective symptom control. Several studies have found discrepancies in

findings when considering only clinical manifestations. For example, one study found that level of lung function impairment was comparable among asthmatics of varying condition (Kelley, Mannino, Homa, Savage-Brown, & Holguin, 2005). In another study, Steele, Meuret, Millard, & Ritz (2012) analyzed trends in only forced expiratory volume per second (FEV_1) and were unable to confirm the association between lung function and asthma severity. The lack of quantified bounds for risk factors is further exacerbated by the variability in practice among different physicians (Chamberlain, Teach, Hayes, Badolato, & Goyal, 2016; Van Sickle, Magzamen, Maenner, Crane, & Corden, 2013).

Table 2. Limitations in current asthma guidelines. While the EPR-3 and GINA report have their respective limitations, the overlapping shortcomings are most implicative of the guidelines' clinical effect. CID=Chronic inflammatory disease, CCDS=Computerized clinical decision support.

EPR-3	GINA report	Both
• Definition of asthma as solely a chronic inflammatory disease • No specification of phenotype categorization or treatment strategy	• Definition of asthma as a chronic inflammatory disease with clusters of weak correlation with specific pathological processes or therapy responses	• Lack of parameters for risk factors • Difficult to incorporate all recommendations into practice • Vague details on guideline integration into CCDS systems

Phenotype-oriented asthma diagnosis

Due to shortcomings in impairment factor-oriented asthma diagnosis, a phenotype-oriented approach has been proposed (Corren, 2013; Wenzel, 2012). By quantifying risk factors unparameterized in the EPR-3 and GINA report guidelines, variability in asthma diagnostics may be reduced (Cowen, Wakefield, & Cloutier, 2007). Despite its potential for yielding more consistent, more personalized, and thus more effective asthma control therapy (Chung, 2016), the approach has not yet been implemented (Bostantzoglou et al., 2015). A phenotype-oriented algorithm may be very resourceful for the efficient and effective diagnosis and management of asthma.

Computerized clinical decision support

Computerized clinical decision support (CCDS) systems are currently automating diagnosis and therapy recommendation to allow clinicians and subspecialists to make quicker and more accurate decisions (Castaneda et al., 2015; Sim et al., 2001). In the case of asthma, studies have found CCDS systems to be effective to varying degree (Fathima, Peiris, Naik-Panvelkar, Saini, & Armour, 2014; Hoeksema et al., 2011; Kuhn et al., 2015; Rigopoulou, Anthracopoulos, Katsardis, & Lymberopoulos, 2013). A CCDS algorithm can be modeled according to phenotype-oriented asthma diagnosis. In order to simulate the results of impairment factor- and phenotype-oriented diagnosis, implemented algorithms may be run against a set of well-defined asthma conditions (Fajt & Wenzel, 2015; Hekking & Bel, 2014).

Methodology

Implementation of EPR-3- and GINA report-based asthma diagnostic algorithms

EPR-3 and GINA report-based guidelines were formatted with the guideline elements model (GEM) Cutter 3 software (Shiffman et al., 2000; Shiffman, Michel, Essaihi, & Thornquist, 2004). The EPR-3 algorithm was designed according to the "Classifying Asthma Severity" and "Assessing Asthma Control" tables (National Heart, Lung, and Blood Institute, National Institutes of Health, 2007, pp. 72-77). The GINA report algorithm was designed according to the "GINA assessment of asthma control in adults, adolescents and children 6-11 years" and "Stepwise approach to control symptoms and minimize future risk" tables (Global Initiative for Asthma, 2017, pp. 29, 43). BlueJ v4.1.0 was used in writing and testing all algorithms (Fig. 1). Algorithm inputs were generated based on averages of lower and upper bounds of the parameterized clinical manifestations (Table 1) outlined in the "Classifying Asthma Severity" and "Assessing Asthma Control" tables in EPR-3.
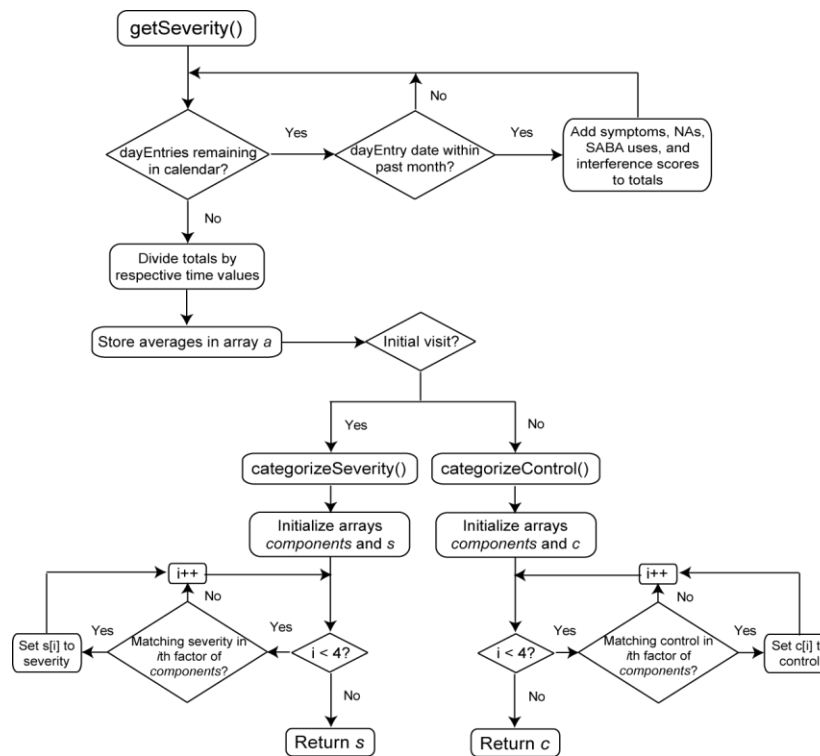

Fig. 1. Flowchart of EPR-3 and GINA report-based algorithms for categorizing asthma severity and control. The getSeverity function iterates through the user's calendar and determines average values for each factor. Depending on whether the user has visited the physician, the categorizeSeverity or categorizeControl function matches the average values with bounds of each factor in the guideline-specific severity or control table, respectively.

Systematic review

The PubMed database was systematically searched in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for systematic review Protocols (PRISMA-P) statement for articles published from January 1, 2007 until September 1, 2017 (Moher et al., 2015). Keywords were "asthma AND (phenotype OR endotype)." Inclusion criteria for articles were as follows: 1) clinical study, 2) comparative study, 3) multicenter study, and 4) observational study. Exclusion criteria were: 1) article not published in English, 2) duplicate article, 3) animal study, 4) pharmacological study, 5) genetic study, and 6) analysis of factors that are not well established in the clinical setting. The most recent search was conducted in October 2017. Meta-synthesis was performed to determine consensual evidence among included studies applicable to the proposed algorithm (Walsh & Downe, 2005). A meta-analysis was not performed due to the wide range of outcome measures from included studies.

Design of phenotype-oriented algorithm and comparison with EPR-3 and GINA algorithms

A computerized algorithm was designed based on meta-synthesis from the systematic review. Factors described as present or absent were addressed by *if* and *then* statements in the algorithm and quantitative bounds were determined based on the most inclusive value from any study. Algorithms for the EPR-3, GINA report, and meta-synthesis were compared with respect to therapy recommendation for five previously defined asthma phenotypes (Lötvall et al., 2011; Wenzel, 2012).

Results/Discussion

Comparison of EPR-3 and GINA report asthma management guidelines

To assess differences between the EPR-3 and GINA report, inputs were generated based on the guidelines' respective age groups and on asthma severity. The algorithms of EPR-3 and GINA report guidelines returned different therapy recommendations (Table 3). In the intermittent severity category, the EPR-3 recommended SABA *pro re nata* while the GINA report recommended low-dose ICS. The GINA report's ICS recommendation is supported by the definition of asthma as a chronic inflammatory disease that is not defined primarily by clinical manifestations. Most notably, the EPR-3 algorithm recommended high dose ICS with LABA and OCS in the severe category compared to specialist assessment in the GINA report algorithm. The definition for asthma has clearly shifted to shape comparatively flexible therapy recommendations for severe asthmatics. It was previously demonstrated that patient-specific treatment, including anti-IL-5 and the anti-IgE omalizumab, yields higher increase in FEV_1 compared to the traditional prescribed ICS/LABA/OCS treatment (Campo et al., 2013; Durham, Caramori, Chung, & Adcock, 2016; Garcia et al., 2013).

Table 3. Preferred therapy recommended by EPR-3 and GINA report guidelines across different severities and age groups. Test cases were based on guideline-defined age groups and asthma severity. SABA=Short acting ß-agonist, ICS=Inhaled corticosteroid, LABA=Long acting ß-agonist, OCS=Oral corticosteroid.

| Guidelines | Age | Severity | | | |
		Intermittent	Mild	Moderate	Severe
EPR-3	0-4	SABA prn	Med. Dose ICS	Med. dose ICS+LABA	High dose ICS+LABA
	5-11	SABA prn	Med. Dose ICS	Med. dose ICS+LABA	High dose ICS+LABA+OCS
	>11	SABA prn	Low dose ICS+LABA	Med. dose ICS+LABA	High dose ICS+LABA+OCS
GINA report	0-5	Low dose ICS	Low dose ICS	Med.-high dose ICS+LABA	Specialist assessment
	>5	Low dose ICS	Low dose ICS+LABA	Med.-high dose ICS+LABA	Specialist assessment

Meta-synthesis from systematic review

A systematic review was conducted through the PubMed database according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) methodology (Fig. 2). The search query used was "asthma AND (phenotype OR endotype)" and identified records were limited to clinical, comparative, multicenter, and observational studies published from Jan. 2007 to Sept. 2017. Records were further narrowed by including filters for full text availability and specificity to humans. Findings for all studies were compiled in a Microsoft Word document and parameters/conditions were in turn compiled separately.
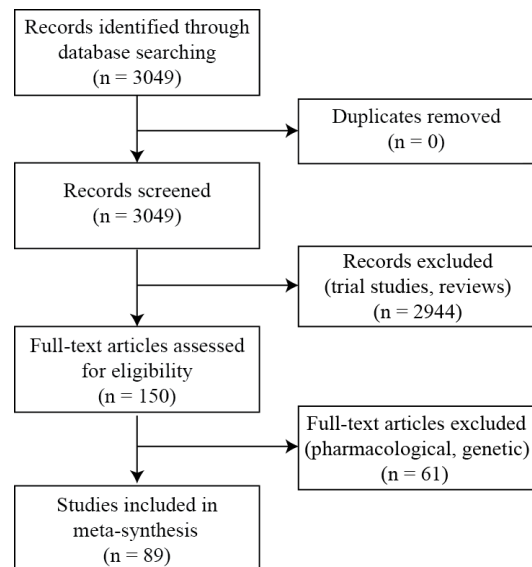

Fig. 2. PRISMA flowchart for systematic review. Articles that pertained to pharmacologic, review, or genetic studies were excluded from meta-synthesis.

Parameters of asthma phenotype categorization

Through the systematic review, data on a number of factors were compiled for meta-synthesis (Table 4). Age of onset, presence of comorbidities, sputum eosinophilia, and atopy were the most frequently identified factors in distinguishing clusters of asthma phenotypes. Multiple studies also found aspirin sensitivity, fractional exhaled nitric oxide (FeNO), serum IgE, and neutrophilia to be potential factors, although some studies did not demonstrate such significant effect. Furthermore, there was a consensus among a number of studies on the impact of asthma-COPD overlap syndrome (ACOS). Several studies found more severe manifestation in the ACOS group compared to the asthma and COPD patient groups (de Marco et al., 2013; Kitaguchi, Yasuo, & Hanaoka, 2016; Menezes et al., 2014; M. Miravitlles,

Barrecheguren, & Román-Rodríguez, 2015; Marc Miravitlles et al., 2013; Marc Miravitlles, Barrecheguren, & Roman-Rodriguez, 2015; Montes de Oca et al., 2016). Based on the findings from cluster analyses of asthma, COPD, and ACOS patients, parameters may be defined for more reliable diagnosis of the severe ACOS phenotype.

Table 4. Identified factors in distinguishing between asthma clusters and phenotypes. Factors are categorized into serum, clinical manifestations, comorbidities, and patient and environmental conditions. FEV1/FVC=forced expiratory volume in 1s/forced vital capacity, QoL=quality of life, ACOS=asthma-COPD overlap syndrome, GERD=gastroesophageal reflux disease.

Serum	Clinical manifestations	Comorbidities	Pt./Environ. conditions
Eosinophilia	FEV_1/FVC	ACOS	Age of onset
Neutrophilia	Airflow obstruction	GERD	Atopy
IgE level	FeNO	Obesity	Smoke exposure
Inflammatory	QoL	Metabolic acidosis	Aspirin sensitization
biomarkers	Sputum eosinophils	Sepsis	Race
		Respiratory infection	

Comparison of EPR-3-, GINA-, and meta-synthesis-based algorithms

The EPR-3-, GINA-, and meta-synthesis-based algorithms were run against the five phenotypes previously defined (Wenzel, 2012) and therapy recommendations were compared (Table 5). According to the outputs of the EPR-3 and GINA algorithms, ICS was recommended in most asthma phenotypes. Despite the efficacy of ICS for long-term asthma control, the late-onset eosinophilic phenotype may be corticosteroid-refractory, implying the need for more targeted therapy. Based on the meta-synthesis-based algorithm, targeted therapy such as anti-IL-5 for late-onset eosinophilia and macrolides for neutrophilia were recommended. While the use of ICS and LABA is effective for most phenotypes, the addition of targeted medication personalizes therapy to a greater degree.

Table 5. Therapy recommended by EPR-3-, GINA-, and meta-synthesis-based algorithms across five common asthma phenotypes.

	Algorithm source		
Phenotype	EPR-3	GINA report	Meta-synthesis
Early-onset allergic	Low-dose ICS+LABA	Low-dose ICS+LABA	Low-dose ICS
Late-onset eosinophilic	Med.-dose ICS+LABA	Med.-high-dose ICS+LABA	Anti-IL-5
Exercise-induced	SABA prn	Low-dose ICS	Low-dose ICS+SABA prn
Obesity-related	Med.-dose ICS+LABA	Med.-high-dose ICS+LABA	Antioxidant, LABA
Neutrophilic	Low-dose ICS+LABA	Low-dose ICS+LABA	Macrolides, LABA

Conclusions

Holistically, the study identified and elucidated differences between the EPR-3 and GINA report guidelines for asthma management. The guidelines' treatment recommendations reflected the shift in definition of asthma over the past decade. Analysis of EPR-3 and the GINA report demonstrated the need for physicians to be cognizant of the heterogeneity of asthma as a disease and the more personalized treatment required to ameliorate asthmatics' response to prescribed medication. While the EPR-3 guidelines defined clear parameters for diagnosis, the GINA report guidelines left leeway for clinicians to adopt a more holistic view of the patient's impairment and risk factors. The meta-analysis in the latter part of the study compiled currently recognized factors contributing to asthma phenotypes. Through comparison of the EPR-3, GINA report, and meta-synthesis-based algorithms, the phenotype-oriented algorithm for asthma diagnostics was implemented and confirmed to recommend targeted therapy.

Identified differences between the EPR-3 and GINA 2017 report may be outlined in the next official guidelines for asthma and recommendations for physicians may shift more toward the phenotype-oriented approach to asthma diagnostics. The reduced variation in asthma diagnostics may be invaluable to both clinicians and patients in the future. Additionally, due to the compilation of results from the systematic review, the newly proposed algorithm may reliably improve upon current asthma diagnostic approaches and prompt more personalized treatment, specifically for severe asthmatics. A major reason for variability in physician practice is the co-existence of multiple asthma diagnosis guidelines (Gupta, Paolucci, Kaplan, & Boulet, 2016) but with the meta-synthesis-based algorithm, therapy recommendations may become more personalized.

In order to elucidate the role of the algorithm in practice, it would be evaluated by clinicians and subspecialists through clinical and multicenter studies. The meta-synthesis-based algorithm may become integrated into clinical decision support systems to recommend more targeted therapy and reduce variability of asthma diagnostics in the future. Additionally, the method followed in the current study may also be extended to other fields and assist physicians in the clinical setting.

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