

Generating evidence to inform an update of asthma clinical practice guidelines: Perspectives from the National Heart, Lung, and Blood Institute

George A. Mensah, MD,^a James P. Kiley, PhD,^b and Gary H. Gibbons, MD^c *Bethesda, Md*

Asthma is the most prevalent chronic respiratory disease worldwide. Its increasing prevalence and evidence of suboptimal control require renewed efforts in the development and widespread implementation of clinical practice guidelines for prevention, treatment, and control. Given the rapidly changing landscape and evolving best practices for guideline development, the National Heart, Lung, and Blood Institute made a commitment to support rigorous systematic evidence reviews that frontline health care providers and stakeholders could use to create new or update existing guidelines. This article describes the protocols, key questions, methodology, and analytic framework to support the update of the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) on the diagnosis and management of asthma in adults and children. It also describes the expert panel's practical experience in managing asthmatic patients across the age and severity spectrum. The article explains the process for ensuring that the expert panel's deliberations are conducted in accordance with the Institute of Medicine's standards and recommendations for guideline development. The outcome of this ambitious effort will be an update of the EPR-3 asthma guidelines and publication of the key recommendations in the *Journal of Allergy and Clinical Immunology*. Importantly, several novel approaches will be explored and incorporated as appropriate to accelerate adoption and sustained implementation of the guidelines. (*J Allergy Clin Immunol* 2018;■■■■:■■■-■■■.)

Key words: Asthma, clinical practice guideline, allergen, bronchial thermoplasty, immunotherapy, inhaled corticosteroids, long-acting muscarinic antagonists

Abbreviations used

AHRQ: Agency for Healthcare Research and Quality

CPG: Clinical practice guideline

EPR-3: National Asthma Education and Prevention Program Expert Panel Report 3

EPR-4 WG: National Asthma Education and Prevention Program Expert Panel Report 4 Working Group

FACA: Federal Advisory Committee

ICS: Inhaled corticosteroid

NAEPP: National Asthma Education and Prevention Program

NHLBI: National Heart, Lung, and Blood Institute

The rapidly changing landscape and evolving best practices for developing clinical practice guidelines (CPGs) provided an opportunity in 2013 for the National Heart, Lung, and Blood Institute (NHLBI) to examine and refocus its agenda in the domain of CPG development.¹ After extensive consultations with internal and external stakeholders and recommendations from the National Heart, Lung, and Blood Advisory Council, the NHLBI made a commitment to primarily support rigorous systematic evidence reviews and evidence syntheses that frontline health care providers, health professional organizations, and relevant stakeholders could use to create new or update existing CPGs.¹ Importantly, the advisory council also recommended NHLBI's continued engagement in the production of CPGs primarily by partnering with professional societies or by creating standalone guidelines if the need is great and there is no other sponsoring organization or group of organizations.¹

The first application of this refocused agenda was in the systematic review reports on blood pressure,² cholesterol,³ cardiovascular risk assessment,⁴ lifestyle interventions,⁵ and overweight and obesity⁶ that informed the development of related cardiovascular CPGs from the American Heart Association, American College of Cardiology, and partner organizations.⁷⁻¹⁰ From this perspective, we first address the increasing national and global burden of asthma and the need for up-to-date guidelines on managing asthma and then explore how the NHLBI-refocused agenda has now been applied for development of asthma CPGs. Specifically, we highlight the process for generating rigorous systematic evidence reviews and evidence syntheses to support the update of the 2007 National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) on the diagnosis and management of asthma in adults.¹¹

From ^aCenter for Translation Research and Implementation Science, ^bDivision of Lung Diseases, and ^cOffice of the Director, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Institutes of Health or the US Department of Health and Human Services.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 30, 2018; revised June 11, 2018; accepted for publication July 12, 2018.

Corresponding author: George A. Mensah, MD, NHLBI/CTRIS, 6705 Rockledge Dr, Suite 6070, Bethesda, MD 20892. E-mail: George.Mensah@nih.gov.

0091-6749/\$36.00

© 2018 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaci.2018.07.004>

THE INCREASING NATIONAL AND GLOBAL BURDEN AND HEALTH CARE COSTS OF ASTHMA

Chronic respiratory diseases, such as asthma, are common and remain major contributors to impaired quality of life, reduced productivity, increased hospitalizations and in-hospital mortality, and increasing health care costs in the United States and worldwide.¹²⁻¹⁴ For example, in 2015, asthma was the most prevalent chronic respiratory disease worldwide and had twice as many prevalent cases as chronic obstructive pulmonary disease.¹² Globally, the prevalence of asthma increased by 13% to more than 358 million persons from 1990 to 2015.¹² In the United States, the prevalence of asthma was estimated at 26 million persons in 2010, about 19 million adults aged 18 years and over and 7 million children aged 17 years or younger.¹⁵ For the period 2008–2010, Akinbami et al¹⁵ estimated that asthma prevalence was higher among children than adults and, compared with white persons, higher among multiple-race, black, and American Indian or Alaska Native persons.¹⁵ Among patients with medically treated asthma, the total annual costs (including medical care, absenteeism, and mortality) is estimated at \$82 billion.¹⁴

Importantly, poorly controlled or uncontrolled asthma is common and associated with increased costs, increased health care use, and decreased economic productivity.¹⁶ For example, using data from the 2008–2010 Medical Expenditure Panel Surveys, Sullivan et al¹⁶ estimated that medical expenditures attributable to asthma were nearly \$4423 greater for patients with uncontrolled asthma compared with those who did not have asthma. Additionally, frequency of hospital discharges was up to 4.6-fold greater, and emergency department visits were nearly 2-fold greater in patients with uncontrolled asthma compared with those without asthma.¹⁶ Thus, timely access to updated CPGs for the treatment and control of asthma and the prevention of future asthma exacerbations is crucial.

NEED FOR AN UPDATED ASTHMA GUIDELINE

In 1989, the NHLBI initiated the National Asthma Education Program, which was subsequently renamed the National Asthma Education and Prevention Program (NAEPP).¹⁷ In addition to its core mission of educating patients, providers, and the public about the signs, symptoms, and seriousness of asthma, the NAEPP has also overseen a strong partnership effort for the development of CPGs for the management of asthma and the creation of related tools and materials to facilitate guideline implementation.

In 1991, the NAEPP produced its first expert panel report on guidelines for the diagnosis and management of asthma.¹⁸ This first CPG underwent a comprehensive update in 1997 and an update of selected topics in 2002.^{19,20} The most current guideline, published in 2007, is the expert panel's third report,¹¹ which was widely acclaimed as a "scientific comprehensive review" of the evidence, as well as a "user-friendly" summary report with recommendations for delivering "the best care possible for both children and adults with asthma."²¹

In 2014, an NHLBI Advisory Council Working Group was tasked with assessing the need for an update of the NAEPP EPR-3 and concluded that one was needed.²² This working group also recommended that the 2007 Expert Panel Report should be updated on selected topics and that the NHLBI should continue to support and coordinate the production of the guidelines through the NAEPP²² similar to the rationale and approach used to publish

the guidelines on sickle cell disease.^{23,24} Six high-priority topics identified for the update included (1) adjustable medication dosing in patients with recurrent wheezing and asthma; (2) long-acting anti-muscarinic agents in asthma management as add-on to inhaled corticosteroids; (3) bronchial thermoplasty in adults with severe asthma; (4) fraction of exhaled nitric oxide in diagnosis, medication selection, and monitoring treatment response in asthmatic patients; (5) remediation of indoor allergens (house dust mites/pets) in asthma management; and (6) immunotherapy and asthma management. Topics 1 and 2 were subsequently combined, resulting in a total of 5 topical categories, as shown in Table I.²⁵⁻²⁹

GENERATING EVIDENCE TO INFORM THE GUIDELINE UPDATE

In alignment with the stated commitment in the refocused agenda, the NHLBI engaged the Agency for Healthcare Research and Quality (AHRQ) and provided support for rigorous systematic evidence reviews through AHRQ Evidence-based Practice Centers. Protocols for the systematic evidence reviews have been published previously.^{25,27-29} The published protocols address formulation of the key questions that merit systematic literature review, the methods used, and the overall analytic framework. Completed systematic evidence review reports have been published on the AHRQ's Web site and include the effectiveness of indoor allergen reduction in the management of asthma³⁰ and the role of bronchial thermoplasty.²⁶ In addition, completed systematic review reports are now published for the effectiveness of indoor allergen reduction in the management of asthma,³¹ the role of immunotherapy in the management of asthma,³² the role of intermittent inhaled corticosteroids and long-acting muscarinic antagonists,³³ and the clinical utility of fraction of exhaled nitric oxide testing in asthmatic patients.³⁴ The critical questions for the systematic review topics are shown in Table I.

CHARTING THE PATH FROM EVIDENCE TO THE GUIDELINE UPDATE

Recently, the NHLBI established the NAEPP Federal Advisory Committee (FACA). The 15-member committee will assist the NHLBI in facilitating the effective exchange of information on asthma activities among federal agencies and partner organizations to enhance coordination of asthma-related programs and activities. The crucial role of the NAEPP and numerous national-level organizations in this endeavor cannot be overemphasized. These strategic partners include major scientific, professional, governmental, lay, and voluntary health organizations committed to advancing the clinical management of asthma. Working groups of the NAEPP FACA will be established to focus on critical topics, such as dissemination and implementation and school health. The National Asthma Education and Prevention Program Expert Panel Report 4 Working Group (EPR-4 WG), which is coordinated, staffed, and supported by the NHLBI, plays the pivotal role in charting the path by taking the evidence generated and developing the guideline update.

The EPR-4 WG will use NHLBI-funded AHRQ evidence reports to update selected topics in the EPR-3 guidelines. The EPR-4 WG will update the clinical recommendations for the selected topics and grade the strength of each recommendation.³⁵ Guideline implementation will be considered while drafting the

TABLE I. Topics and key questions addressed in the systematic evidence reviews

	Topics	Key questions addressed in the systematic review
1	Intermittent use of ICSs and long-acting muscarinic antagonists for asthma ²⁵	● What is the comparative effectiveness of an intermittent ICS compared with no treatment and pharmacologic or nonpharmacologic therapy in children 0 to 4 years old with recurrent wheezing? ● What is the comparative effectiveness of an intermittent ICS compared with ICS controller therapy in patients 5 years of age and older with persistent asthma? ● What is the comparative effectiveness of an ICS with a LABA used as both controller and quick-relief therapy compared with an ICS with or without a LABA used as controller therapy in patients 5 years of age and older with persistent asthma? ● What is the comparative effectiveness of a LAMA as add-on therapy to an ICS controller therapy compared with placebo or increased ICS dose in patients 12 years of age and older with uncontrolled persistent asthma? ● What is the comparative effectiveness of a LAMA compared with other controller therapy as add-on therapy to an ICS in patients 12 years of age and older with uncontrolled persistent asthma? ● What is the comparative effectiveness of a LAMA as add-on therapy to an ICS plus a LABA compared with an ICS plus a LABA as controller therapy in patients 12 years of age and older with uncontrolled persistent asthma?
2	Effectiveness and safety of bronchial thermoplasty in asthma management ²⁶	● What are the benefits and harms of using bronchial thermoplasty in the treatment of adult (≥18 years) patients with severe asthma in addition to standard treatment?
3	Fraction of exhaled nitric oxide clinical utility in asthma management ²⁷	● What is the clinical utility of FENO measurements in the management of asthma in addition to or instead of other tests that might be performed? Specifically: ○ What is the diagnostic accuracy of FENO measurement(s) for making the diagnosis of asthma in subjects aged 5 years and older? ○ What is the clinical utility of FENO measurements in monitoring disease activity and asthma outcomes in patients with asthma aged 5 years and older? ● What is the clinical utility of FENO measurements to select medication options (including steroids) for subjects aged 5 years and older? ○ What is the clinical utility of FENO measurements to monitor response to treatment in subjects aged 5 years and older? ○ In children aged 0-4 years with recurrent wheezing, how accurate is FENO testing in predicting the future development of asthma at age 5 years and greater?
4	Effectiveness of indoor allergen reduction in asthma management ²⁸	● Among patients with asthma, what is the effectiveness of interventions to reduce or remove exposure to indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes? ○ What is the effectiveness of carpet removal or cleaning? ○ What is the effectiveness of covers for pillows, mattresses, or furniture and laundering of linens? ○ What is the effectiveness of pest elimination, pet removal, and pet bathing? ○ What is the effectiveness of air purifiers, mold removal, moisture reduction, ventilation, and insulation? ○ What is the effectiveness of multicomponent interventions that include more than 1 strategy and/or affect more than 1 allergen?
5	The role of immunotherapy and asthma management ²⁹	● What is the evidence for the efficacy of SCIT in the treatment of asthma? ○ Does this vary among subpopulations of interest? Does this vary by setting? ■ Clinic ■ Home ● What is the evidence for the safety of SCIT in the treatment of asthma? ○ Does this vary among subpopulations of interest? Does this vary by setting? ■ Clinic ■ Home ● What is the evidence for the efficacy of SLIT in tablet and aqueous form for the treatment of asthma? ○ Does this vary among subpopulations of interest? Does this vary by setting? ■ Clinic ■ Home ● What is the evidence for the safety of SLIT in tablet and aqueous form for the treatment of asthma? ○ Does this vary among subpopulations of interest? Does this vary by setting? ■ Clinic ■ Home

FENO, Fraction of exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

recommendations.³⁶ The EPR-4 WG will present updates to the NAEPP FACA committee in public meetings. The draft guideline report will undergo peer review and be available for public comments in advance of publication.

The EPR-4 WG will be composed of knowledgeable clinician-scientists with practical experience managing asthmatic patients across the age and severity spectrum. The working group will break into smaller groups as needed around the selected topics to

develop clinical recommendations. The EPR-4 WG will meet both in person and through online meetings and follow the Institute of Medicine's recommendations and standards for using systematic evidence reviews in the development of trustworthy guidelines.³⁷ All EPR-4 WG members will follow financial disclosure and conflict of interest procedures using the standard author disclosure procedures outlined for manuscripts submitted to the *Journal of Allergy and Clinical Immunology*³⁸ and follow current best practices and standards for transparency and management of conflicts of interest, as recommended in the Institute of Medicine report.³⁷ The outcome of this sizable effort will be an update of the EPR-3 asthma guidelines and publication of the key recommendations in the *Journal of Allergy and Clinical Immunology*. Furthermore, novel approaches will be explored and incorporated, as appropriate, to facilitate guideline uptake, dissemination, and sustained implementation.

CONCLUSIONS

Developing or updating CPGs is a complex, costly, and time-consuming process with many steps to ensure the validity, credibility, and robustness of the evidence to help guide practitioners, in this case on the optimal means to diagnose, treat, and manage asthmatic patients. These guidelines provide the critical step of truly translating discoveries into better health for all people. This rigorous process is necessary to make certain that clinical care is anchored in a solid evidence base and that taxpayer investment in National Institutes of Health-funded research is informing medical practice. As part of this process, and in addition to use of the published systematic evidence reviews, the expert panel will actively examine the overall asthma management for opportunities for improvement, as well as identify gaps in evidence and implementation to inform future research.

The NHLBI has had a long history of producing practice guidelines and through our refocused approach will continue to partner with all stakeholders to fill the need for heart, lung, and blood guidelines, where indicated. However, the NHLBI cannot stand alone in this area. All stakeholders must be involved and fully endorse and take an active role in implementing the best practices outlined in the guidelines. At the NHLBI, we look forward to working in partnership with the scientific community and related professional societies to ensure we chart a future of turning discoveries into improved health for all.

We thank our colleagues, Dr Michael Engelgau, Ms Janet de Jesus, Ms Sue Shero, and Dr Nakela Cook, who provided constructive comments on an earlier version of this perspective.

REFERENCES

- Gibbons GH, Shurin SB, Mensah GA, Lauer MS. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol* 2013;62:1396-8.
- National Heart, Lung, and Blood Institute. Management of Blood Pressure in Adults: Systematic Evidence Review From the Blood Pressure Expert Panel. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- National Heart, Lung, and Blood Institute. Management of Blood Cholesterol in Adults: Systematic Evidence Review From the Cholesterol Expert Panel. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- National Heart, Lung, and Blood Institute. Assessing Cardiovascular Risk: Systematic Evidence Review From the Risk Assessment Work Group. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- National Heart, Lung, and Blood Institute. Lifestyle Interventions to Reduce Cardiovascular Risk: Systematic Evidence Review From the Lifestyle Work Group. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- National Heart, Lung, and Blood Institute. Managing Overweight and Obesity in Adults: Systematic Evidence Review From the Obesity Expert Panel. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2960-84.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(suppl):S49-73.
- Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2889-934.
- Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol* 2014;63:2985-3023.
- Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691-706.
- Kaur BP, Lahewala S, Arora S, Agnihotri K, Panaich SS, Secord E, et al. Asthma: hospitalization trends and predictors of in-hospital mortality and hospitalization costs in the USA (2001-2010). *Int Arch Allergy Immunol* 2015;168:71-8.
- Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008-2013. *Ann Am Thorac Soc* 2018;15:348-56.
- Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief* 2012;(94):1-8.
- Sullivan PW, Slejko JF, Ghushchyan VH, Sucher B, Globe DR, Lin SL, et al. The relationship between asthma, asthma control and economic outcomes in the United States. *J Asthma* 2014;51:769-78.
- National Institutes of Health. The NIH Almanac: Legislative Chronology. Washington (DC): National Institutes of Health; 2017.
- National Heart, Lung, and Blood Institute, National Asthma Education Program. Guidelines for the diagnosis and management of asthma. Expert Panel Report. *J Allergy Clin Immunol* 1991;88:425-534.
- National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. Bethesda: National Institutes of Health/National Heart, Lung, and Blood Institute; 1997. National Institutes of Health publication no 97-4051.
- National Asthma Education and Prevention Program. Expert Panel Report: guidelines for the diagnosis and management of asthma update on selected topics—2002. *J Allergy Clin Immunol* 2002;110(suppl):S141-219.
- Busse WW, Lemanske RF Jr. Expert Panel Report 3: moving forward to improve asthma care. *J Allergy Clin Immunol* 2007;120:1012-4.
- National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group. Draft Needs Assessment Report for Potential Update of the Expert Panel Report-3 (2007): Guidelines for the Diagnosis and Management of Asthma. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- Yawn BP, Buchanan GR, Afeniyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014;312:1033-48.
- National Heart, Lung, and Blood Institute. Evidence-based Management of Sickle Cell Disease: Evidence Report. Washington (DC): National Institutes of Health/National Heart, Lung, and Blood Institute; 2014.
- Agency for Healthcare Research and Quality. Systematic Review of Intermittent Inhaled Corticosteroids and of Long-acting Muscarinic Antagonists for Asthma. Rockville (MD): Agency for Healthcare Research and Quality; 2016.

26. D'Anci KE, Lynch MP, Leas BF, Apter AJ, Bryant-Stephens T, Kaczmarek JL, et al. Effectiveness and safety of bronchial thermoplasty in management of asthma. Comparative Effectiveness Review No. 202. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-00005-I.) Rockville (MD): Agency for Healthcare Research and Quality; 2017.
27. Agency for Healthcare Research and Quality. Fractional Exhaled Nitric Oxide Clinical Utility in Asthma Management. Rockville (MD): Agency for Healthcare Research and Quality; 2016.
28. Agency for Healthcare Research and Quality. The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma. Research protocol. Rockville (MD): Agency for Healthcare Research and Quality; 2017.
29. Agency for Healthcare Research and Quality. The Role of Immunotherapy and the Management of Asthma: Systematic Review Research Protocol. Rockville (MD): Agency for Healthcare Research and Quality; 2016.
30. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Schoelles K, Umscheid CA. Effectiveness of indoor allergen reduction in management of asthma. Comparative Effectiveness Review No. 201. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-0005-I.) Rockville (MD): Agency for Healthcare Research and Quality; 2018.
31. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in the management of asthma: a systematic review. *J Allergy Clin Immunol* 2018;141:1854–69.
32. Lin SY, Azar A, Suarez-Cuervo C, Diette GB, Brigham E, Rice J, et al. The role of immunotherapy in the treatment of asthma. Comparative Effectiveness Review No. 196 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2015-00006-I). Rockville (MD): Agency for Healthcare Research and Quality; 2018. AHRQ Publication No. 17(18)-EHC029-EF.
33. Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, et al. Intermittent inhaled corticosteroids and long-acting muscarinic antagonists for asthma. Comparative Effectiveness Review No. 194. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012-I). Rockville (MD): Agency for Healthcare Research and Quality; 2018.
34. Wang Z, Pianosi PT, Keogh KA, Zaiem F, Alsawas M, Alahdab F, et al. The diagnostic accuracy of fractional exhaled nitric oxide testing in asthma: a systematic review and meta-analyses. *Mayo Clin Proc* 2018;93:191-8.
35. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35.
36. Chan WV, Pearson TA, Bennett GC, Cushman WC, Gaziano TA, Gorman PN, et al. ACC/AHA Special Report: Clinical practice guideline implementation strategies: a summary of systematic reviews by the NHLBI Implementation Science Work Group: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;69:1076-92.
37. Institute of Medicine (IOM). Clinical Practice Guidelines We can Trust. Washington (DC): National Academies Press; 2011.
38. Journal of Allergy and Clinical Immunology. Information for Authors. Milwaukee: Journal of Allergy and Clinical Immunology; 2018.