2020 FOCUSED UPDATES TO THE Asthma Management Guidelines

A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group

U.S. Department of Health and Human Services
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Reported Disclosures and Conflicts of Interest

Development of this report was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Members of the Expert Panel Working Group ("Expert Panel") of the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC) completed financial disclosure forms and disclosed relevant financial interests described as conflicts of interest to each other prior to their discussions. Members of the Expert Panel were volunteers and received compensation only for travel expenses related to the panel's in-person meetings.

Dr. Cloutier reported that a family member was employed by Regeneron. The Expert Panel did not discuss any Regeneron or related products. Dr. Cloutier was not recused from any Expert Panel discussions.

Dr. Baptist received grant funding from Novartis, AstraZeneca, Teva Pharmaceuticals Industries Ltd. (Teva), and Takeda. Dr. Baptist was recused from drafting, discussing, or voting on sections of the report related to the inhaled corticosteroid recommendations.

Dr. Blake received personal fees from Teva for participation on its Digital Technology Advisory Board and study drugs from Boehringer Ingelheim and GlaxoSmithKline for federally funded clinical trials. Dr. Blake was not recused from any Expert Panel discussions.

Dr. Brooks served on the Scientific Advisory Board for United Allergy Services until December 2019. Dr. Brooks was recused from the initial drafting, discussions, and voting related to the immunotherapy recommendations. However, Dr. Brooks participated in the final voting, discussions, and writing of this section of the report.

Dr. Bryant-Stephens received mattress covers and air purifiers from the Asthma and Allergy Foundation of America. Dr. Bryant-Stephens was not recused from any Expert Panel discussions.

Dr. DiMango participated in an advisory board meeting for AstraZeneca and reported that a family member was formerly employed by Regeneron. Dr. DiMango was not recused from any Expert Panel discussions.

Dr. Dixon received a study medication from MitoQ. Dr. Dixon also received assistance from a medical writer from Boehringer Ingelheim for a manuscript published in 2019 that was not related to the update topics. Dr. Dixon was not recused from any Expert Panel discussions.

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Dr. Schatz received grant funding from Merck, Teva, and ALK-Abello, Inc. Dr. Schatz was recused from the writing, discussion, and voting related to the immunotherapy recommendations.

Dr. Skolnik received personal fees and nonfinancial support from AstraZeneca and personal fees from Teva, Eli Lilly and Company, Boehringer Ingelheim, Merck, Sanofi, Janssen Pharmaceuticals, Intarcia Therapeutics, GlaxoSmithKline, and Mylan. Dr. Skolnik was recused from the writing, discussion, and voting related to the inhaled corticosteroids and LAMA recommendations. Dr. Skolnik withdrew from the Expert Panel on October 1, 2019.

Dr. Stout received a training grant from the Patient-Centered Outcomes Research Institute that distributed pillow and mattress dust covers, nonfinancial support for a new quality review design for the EasyOne Air spirometer, and nonfinancial support for a smartphone spirometer application from Google and development of an asynchronous and an abridged asynchronous online spirometer training course. Dr. Stout was not recused from any Expert Panel discussions.

Dr. Teach had no conflicts of interest to report. Dr. Teach was not recused from any Expert Panel discussions.

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Dr. Walsh had no conflicts of interest to report. Dr. Walsh was not recused from any Expert Panel discussions. Dr. Walsh withdrew from the Expert Panel on October 29, 2019.

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Preface

This report was developed by an Expert Panel Working Group ("Expert Panel") of the National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), presented to the NAEPPCC for the full committee's consideration, and adopted by the NAEPPCC during a public meeting. The NAEPPCC is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

The NHLBI is pleased to present this update, in which several changes to the approaches used in prior NAEPPCC expert panel reports have been implemented. Specifically:

- The decision to update *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3) and the selection of topics to update was initiated by engaging the public with a request for information, rather than relying solely on the National Asthma Education and Prevention Program for these decisions.
- To use the most rigorous methods for gathering information for the focused update, the Agency for Healthcare Research and Quality conducted systematic reviews.
- A consultant with expertise in GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology guided the Expert Panel members in their deliberations and development of the recommendations based on the systematic review reports.

In this report, which was adopted by the NAEPPCC, the Expert Panel has included practical implementation guidance for each recommendation that incorporates findings from NHLBI-led focus groups. These focus groups included people with asthma, caregivers, and providers. To assist providers in integrating these recommendations into the care of patients, the new recommendations have been integrated into the EPR-3 step diagram format. Overall, a highly rigorous process was undertaken to facilitate the development of the evidence-based recommendations and supporting information in this report for use by stakeholders to improve asthma management.

This report was developed under the leadership of Dr. Michelle Cloutier, Expert Panel chair. The NHLBI is grateful for the tremendous dedication of time and outstanding work of all members of the Expert Panel in developing this report. Appreciation is also extended to the NAEPPCC as well as other stakeholder groups (professional societies, health care organizations, government agencies, consumer and patient advocacy organizations, and companies) for their invaluable comments during the public review period. These comments helped enhance the scientific credibility and practical utility of this document.

Ultimately, broad change in clinical practice depends on the uptake, adoption, and implementation of clinical practice recommendations by primary care providers with input from people who have asthma and their families, as well as support from health care systems. This update can serve as a basis to disseminate and facilitate adoption of the asthma recommendations at all levels and to ensure optimal care and equitable outcomes for all individuals with asthma. We ask for the assistance of every stakeholder in reaching our goal: improving asthma care and the quality of life of every person with asthma.

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Foreword

It has been 13 years since the last revision of the asthma recommendations, and substantial progress has been made since that time in understanding the origins of asthma as well as its pathophysiology and treatment. As members of the pulmonary and allergy provider community and the primary care community that provide more than half of all asthma care in the United States, we now recognize that asthma is not one disease, but it is a syndrome composed of multiple phenotypes. Asthma is much more complex than indicated in the *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma* (EPR-1),[1] released in 1991, which characterized asthma as an inflammatory disease that is responsive to corticosteroids.

This document updates selected topics that were identified as high priority by an NHLBI Advisory Council Asthma Expert Working Group based on input from previous guideline developers, National Asthma Education and Prevention Program (NAEPP) participant organizations, and the public. The list of these priority topics was published in 2015.[2]

Seventeen topics were suggested initially for updating, and six topics were found to have sufficient new information to warrant an update. Key questions were drafted by the Advisory Council and used by Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers to conduct systematic reviews that were published between October 2017 and March 2018.[3-7] The Expert Panel was then assembled in July 2018 and charged with using these systematic reviews to develop recommendations on these six previously chosen topics.

The Expert Panel updated the literature for the systematic reviews through October 2018 and then developed its recommendations. These recommendations differ from other guidelines in several important ways:

- The key questions were developed a priori and not after a review of the current literature.
- The Expert Panel was composed of diverse individuals not only from the asthma specialty community (adult and pediatric pulmonary and allergy specialists), but also from the general medical community (pediatric, internal medicine, family medicine, and emergency medicine providers). Expert Panel members also included health policy and dissemination and implementation experts, and the panel received input from patients and families.
- The Expert Panel members abided by strict standards for conflicts of interest developed by the Institute of Medicine (now the National Academy of Medicine)[8] and in the spirit of the more recently released recommendations from the American College of Physicians.[9] Individuals with any conflict of interest related to the updated topics recused themselves from discussions of those topics.
- This was the first time that the NAEPP used GRADE methodology (discussed below) to provide transparency in the decision-making process.
- Lastly, but not insignificantly, the Expert Panel sought comments from external groups and individuals, including from the NAEPP Coordinating Committee (whose members represent a diverse group of stakeholders), the public, and federal agencies. Although the panel that developed the *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3) also sought external input, this approach has rarely been used by other asthma guideline committees. The Expert Panel considered this input when it developed the final recommendations and this document.

The methodology framework used for this update, GRADE, is the internationally recommended approach for developing recommendations that clinicians can trust. This framework endorses a systematic and transparent approach to decision-making, uses established criteria to rate the certainty of evidence, and determines the strength of the recommendations. Recommendations developed using GRADE combine certainty of evidence with patient values and preferences and weigh the benefits and harms of making treatment recommendations. Importantly, the recommendations are based on the key questions that clinicians, both generalists and specialists, wanted to be answered.

Users of these recommendations may be disappointed by the absence of many strong recommendations—that is, recommendations that clinicians should adhere to for almost all individuals with asthma as the standard of care. This is not, however, surprising given the variations in asthma phenotypes and endotypes and in the outcomes used in the studies reviewed to develop the recommendations. When the GRADE framework is used, randomized controlled trials are initially rated as offering a high certainty of evidence, but issues with study designs (e.g., lack of blinding or of a placebo control), heterogeneity of study results, or small numbers of events may result in downgrading the certainty of evidence. For most of the asthma recommendations, the overall certainty of the evidence was downgraded because of inconsistencies in study results, risk of bias, or absence of critical standardized outcome measures. The need to downgrade the evidence should be a clarion call to investigators to use standardized and validated outcome measures that were outlined in the Asthma Outcomes Workshop (2012).[10] This single activity will create more robust evidence to support recommendations in the future.

The working group that identified the six priority topics for this update based its recommendations on information available at that time. This information did not include the subsequent explosion of research and U.S. Food and Drug Administration approval of multiple drugs classified as asthma biologics. Any attempt to include biologic agents in this report at the start of this effort would have delayed the release of these recommendations for another 1 to 2 years, and this was felt to be unacceptable. This update also is not a complete revision of EPR-3. Important aspects of care, such as asthma education (including inhaler technique) and assessment tools for asthma control, adherence, and other factors are not covered. Reasons for these limitations included lack of time, lack of resources, and, for some topics, insufficient new evidence.

Finally, several new features in this update were designed to aid providers and clinicians in addressing these topics with their patients. The biggest of these changes is the addition of an implementation guidance section for each recommendation. Each implementation guidance section begins with a clinician summary—an expanded statement of the recommendation to quickly assist clinicians in better understanding the recommendation from a user's perspective. The implementation guidance section also provides further clarification of the population to which the recommendation applies, exceptions, and practical aspects of how to use the recommendation in patient care. At the end of each implementation guidance section is a list of issues suggested by the Expert Panel to communicate to patients as part of shared decision-making about whether to use the therapy or intervention mentioned in the recommendation. Amended step diagrams for asthma management are also provided for the topics being updated. Many of the updated interventions in these diagrams are now preferred first-line treatments.

Moving forward, the process of guideline development needs to be more agile. Creating an ongoing process for developing recommendations that includes individuals with varied expertise and from multiple organizations may facilitate this process. In addition, the structure of the recommendations may need to change. The step diagrams, although useful, are a one-size-fits-all approach. The current recommendations use a patient-centered approach that is critical but not sufficient. In the emerging era of personalized medicine, tailored interventions and treatments customized to particular individuals with specific characteristics will be needed. Discussions about how to address individualized approaches to asthma care and how to incorporate those approaches into the standard of care are needed now so that future recommendations can integrate these new approaches.

Finally, I would like to thank the members of the Expert Panel who voluntarily gave their time and expertise to complete this work. The amount of work that was needed in a compressed period of time from each member was very high. To them, to Drs. Kiley and Mensah, whose support was unwavering, and to the NHLBI and Westat staff, thank you.

Michelle M. Cloutier, M.D.

Chair, Expert Panel

Acronyms and Abbreviations

ACP	American College of Physicians
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
API	Asthma Predictive Index
AQLQ	Asthma-Related Quality of Life Questionnaire
BELT	Blacks and Exacerbations on LABA vs. Tiotropium study
BT	bronchial thermoplasty
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
ED	emergency department
EIB	exercise-induced bronchoconstriction
EPC	Evidence-Based Practice Center
EPR	Expert Panel Report
FDA	U.S. Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
GI	gastrointestinal
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HEPA	high-efficiency particulate air (a type of filter)
ICS	inhaled corticosteroid
ICS-LABA	inhaled corticosteroid and long-acting $beta_2$-agonist combination, typically in a single device

Ig	immunoglobulin (e.g., immunoglobulin E [IgE] and similar types, such as IgG)
IL	interleukin (e.g., interleukin-4 [IL-4], and similar types, such as IL-12)
IT	immunotherapy
LABA	long-acting $beta_2$-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
MID	minimally important difference
NAEPP	National Asthma Education and Prevention Program
NHLBAC	National Heart, Lung, and Blood Advisory Council
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OR	odds ratio
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
ppb	parts per billion
PRN	pro re nata (Latin for “as needed”)
RCT	randomized controlled trial
RR	relative risk
RTI	respiratory tract infection
SABA	short-acting $beta_2$-agonist
SAE	serious adverse event
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
SMART	single maintenance and reliever therapy
T2	type 2
URTI	upper respiratory tract infection

SECTION I

Introduction

Background and Rationale for Focused Updates

In 1989, the National Heart, Lung, and Blood Institute (NHLBI) created a program, now known as the National Asthma Education and Prevention Program (NAEPP), to address asthma issues in the United States. The NAEPP focuses on raising awareness and ensuring appropriate diagnosis and management of asthma to reduce asthma-related morbidity and mortality and to improve the quality of life of individuals with asthma. To that end, the NAEPP published its first expert panel report (EPR) on the diagnosis and management of asthma in 1991.[1] A comprehensive revision, EPR-2, was published in 1997,[11] followed by an update of selected topics in 2002 and then a third expert panel report, EPR-3, in 2007.[12]

In 2014, the Asthma Expert Working Group of the National Heart, Lung, and Blood Advisory Council (NHLBAC) completed an assessment of the need to revise the NAEPP's *Expert Panel Report-3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3)[12] and the content of such a revision. After a discussion and review of the responses to a public request for information on the need for and potential content of an update, the NHLBAC Asthma Expert Working Group (which included members of the EPR-3 expert panel) determined that a focused update on six priority topics was warranted. For each of the six priority topics, the NHLBAC Asthma Expert Working Group determined the key questions to address in the systematic reviews. For each key question, the working group of the NHLBAC identified the patient population, intervention, relevant comparators, and outcomes of interest.

The six priority topics identified for systematic review were as follows:

1. Fractional exhaled nitric oxide (FeNO) in diagnosis, medication selection, and monitoring of treatment response in asthma
2. Remediation of indoor allergens (e.g., house dust mites/pets) in asthma management
3. Adjustable medication dosing in recurrent wheezing and asthma
4. Long-acting antimuscarinic agents in asthma management as add-ons to inhaled corticosteroids
5. Immunotherapy and the management of asthma
6. Bronchial thermoplasty (BT) in adult severe asthma

The NHLBAC Asthma Expert Working Group recommended that another 11 topics be acknowledged in the update but that no recommendations be developed for these topics because of the lack of sufficient new data for a systematic review of these topics at that time.[12] These emerging topics are as follows:

- Adherence
- Asthma action plans
- Asthma heterogeneity
- Biologic agents
- Biomarkers (other than FeNO)
- Classification of asthma severity
- Long-acting $beta_2$-agonist (LABA) safety
- Physiological assessments
- Prevention of asthma onset
- Role of community health workers in asthma management
- Step-down from maintenance therapy

The Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers (EPCs) conducted systematic reviews of the six priority topics and published the findings from these reviews online between October 2017 and March 2018.[3-7] These systematic reviews provided the evidence used to update the priority topics for this report.

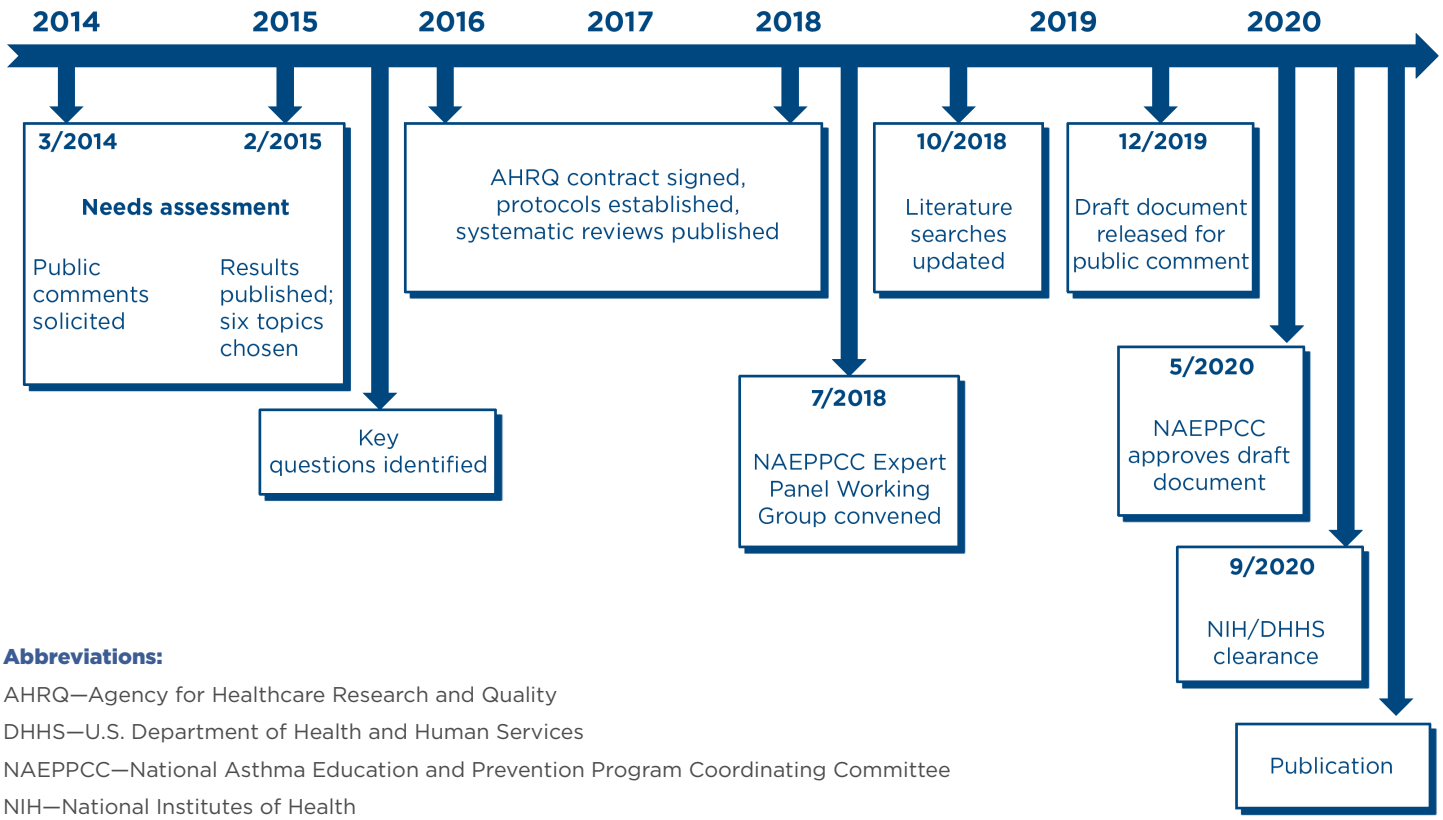
In 2015, the NAEPP Coordinating Committee (NAEPPCC), which is a Federal advisory committee, was created to continue the work of the NAEPP. In 2018, after the systematic reviews on the priority topics were completed, the NAEPPCC established the Expert Panel Working Group (hereafter referred to as the "Expert Panel"), which was charged with using the published systematic review reports to make recommendations on the key questions that could be implemented by health care providers and people with asthma.

The Expert Panel, composed of 18 members and a chair, included asthma content experts, (pediatric and adult pulmonologists and allergists, an emergency room physician, and a pharmacist), primary care clinicians (pediatric, internal medicine, and family medicine providers), health policy experts, and implementation and dissemination experts. The Expert Panel received support from individuals who had experience using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[13]

While the Expert Panel considered its recommendations, the NHLBI convened focus groups made up of diverse asthma management stakeholders, including individuals with asthma, caregivers, and health care providers. These focus groups provided input on participants' preferences and valuations of various asthma outcomes and interventions. The Expert Panel used summaries of these focus group discussions to inform its recommendations.

The Expert Panel initially presented its draft recommendations for comment and review to the NAEPPCC. The draft recommendations were also issued for public comment as well as for input from Federal agencies. The Expert Panel considered all comments received and incorporated many of them into this final report. The NAEPPCC adopted the Expert Panel's report during a public meeting and recommended the updated guidelines to HHS. Following review and clearance, HHS approved the updated guidelines, which were subsequently published in the *Journal of Allergy and Clinical Immunology*. A timeline of the steps completed to produce this report, beginning with the needs assessment, is shown in Figure I.a.

Figure I.a: Timeline for 2020 Asthma Guideline Update



Abbreviations:

AHRQ—Agency for Healthcare Research and Quality

DHHS—U.S. Department of Health and Human Services

NAEPPCC—National Asthma Education and Prevention Program Coordinating Committee

NIH—National Institutes of Health

Methods

Four AHRQ EPCs conducted and published systematic review reports on the key questions for the six priority topics. The pharmacologic topics (adjustable medication dosing and long-acting muscarinic antagonists) were combined into a single systematic review; therefore, five systematic review reports were prepared on the six priority topics:

- **The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management** (https://doi.org/10.23970/AHRQEPCCER197)
- **Effectiveness of Indoor Allergen Reduction in Management of Asthma** (https://doi.org/10.23970/AHRQEPCCER201)
- **Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma** (https://doi.org/10.23970/AHRQEPCCER194)
- **Role of Immunotherapy in the Treatment of Asthma** (https://doi.org/10.23970/AHRQEPCCER196)
- **Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma** (https://doi.org/10.23970/AHRQEPCCER202)

Systematic Reviews of the Literature

The protocols[3-7] that the EPCs used in their systematic reviews describe the prespecified key questions that they addressed (listed in Table I.a), the methods they used, and the overall analytic framework.

Table I.a: Systematic Review Key Questions

Topic	Key question
FeNO	What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 years and older?
	What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 years and older?
	What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 years and older?
	What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 years and older?
	In children ages 0–4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 years and above?
Allergen mitigation	Among individuals with asthma, what is the effectiveness of interventions to reduce or remove exposures to indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes?

Topic	Key question
ICS	What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic, or nonpharmacologic therapy in children 0–4 years with recurrent wheezing?
	What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in individuals 5 years of age and older with persistent asthma?
	What is the comparative effectiveness of ICS with LABA used as both controller and quick-relief therapy compared to ICS with or without LABA used as controller therapy in individuals 5 years of age and older with persistent asthma?
LAMA	What is the comparative effectiveness of LAMA compared to other controller therapy as add-on to ICS in individuals ages 12 years and older with uncontrolled, persistent asthma?
	What is the comparative effectiveness of LAMA as add-on to ICS controller therapy compared to placebo or increased ICS dose in individuals ages 12 years and older with uncontrolled, persistent asthma?
	What is the comparative effectiveness of LAMA as add-on to ICS-LABA compared to ICS-LABA as controller therapy in individuals ages 12 years and older with uncontrolled, persistent asthma?
Immunotherapy	What is the evidence for the efficacy of SCIT in the treatment of asthma?
	What is the evidence for the safety of SCIT in the treatment of asthma?
	What is the evidence for the efficacy of SLIT, in tablet and aqueous form, for the treatment of asthma?
	What is the evidence for the safety of SLIT, in tablet and aqueous form, for the treatment of asthma?
BT	What are the benefits and harms of using BT in addition to standard treatment for the treatment of individuals ages 18 years and older with asthma?

Abbreviations: BT, bronchial thermoplasty; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

When conducting the systematic reviews, the EPCs sought studies that included the prespecified target population(s) and settings and that used the prespecified interventions, comparators, and outcomes. The EPCs excluded articles about studies that did not meet the inclusion criteria listed in the protocols for each systematic review. These inclusion criteria were summarized in the published systematic review reports. (Appendices to the systematic review reports documented the rationales for excluding published articles identified by a broad search of the literature.) The systematic review reports also included the EPCs' assessments of the risk of bias of each included article and of the strength of evidence for each key question using methods described in the protocols and systematic review reports. The EPCs were not required to use GRADE methodology to conduct the systematic reviews, but they used a similar framework. After peer review and posting for public comment, the systematic review reports were finalized and published between late 2017 and early 2018.

Updated Reviews of the Literature

Westat (contract #HHSN268201700020B) conducted a literature search to identify any new articles published between the completion of the EPCs' systematic review literature searches and October 2018, when the Expert Panel began its work. The search strategies and the inclusion and exclusion criteria used in the updated literature searches were as similar as possible to those used in the initial systematic reviews. After reviewing the results of the updated literature searches, the Expert Panel determined that 15 additional articles addressing specific aspects of the key questions should be included in the focused update. The new articles were assessed for risk of bias. The Expert Panel considered the new evidence in conjunction with the evidence from the systematic review reports, but the new evidence was not incorporated into the pooled estimates in the evidence to decision (EtD) tables.

Expert Panel Processes

Team Structure

The Expert Panel met both in person and via webinar. In addition to their collective efforts, each panel member was assigned to one of six teams to address the topic-specific key questions identified by the NHLBAC Asthma Expert Working Group. Each topic team consisted of at least one content expert, primary care clinician, and individual with implementation expertise; some topic team members had multiple areas of expertise. The Integration and Implementation Team, composed of one representative from each of the topic teams, was tasked with integrating the new recommendations into the step diagrams from EPR-3 to create visual summaries of these steps. The NHLBI assembled and coordinated the Expert Panel. Westat provided technical and support services, including a methodology team with expertise in GRADE.

Disclosure of Conflicts of Interest and Conflict Management

To identify and manage potential conflicts of interest (COIs), the Expert Panel complied with the Institute of Medicine (now National Academy of Medicine) recommendations and standards for using systematic, evidence-based reviews to develop trustworthy guidelines. The Expert Panel also followed the spirit of the recommendations for guideline panels that the American College of Physicians (ACP) published in August 2019, midway through the development of these asthma guidelines.[8,9,14] Where possible, the Expert Panel implemented many of the new ACP guideline panel recommendations.

All Expert Panel members made financial disclosures and reported COIs using the standard author disclosure procedures described by the International Committee of Medical Journal Editors for manuscripts submitted to the *Journal of Allergy and Clinical Immunology* (JACI); the JACI editors reviewed these COI reports.[15] Expert Panel members disclosed all personal fees, grant support,

and nonfinancial support received, including support from entities that could be perceived to have influenced or could potentially have influenced the work of the Expert Panel for the past 36 months. They reported these COIs in writing before the Expert Panel initially convened, before each face-to-face meeting, and at the completion of the guidelines. In keeping with JACI requirements, these disclosure reports did not include sources of research funding, such as government agencies, charitable foundations, or academic institutions.

The Expert Panel chair and JACI editors rated each COI as high, moderate, or low and used a modified version of the ACP recommendations to develop a plan to manage each level of COI. For the Expert Panel, a high COI was defined as multiple interactions with biomedical entities (drug, biotechnology, or medical device companies) and could include interactions that were related or not related to the six priority topics. Participation in any speakers bureau of any biomedical entity was also considered a high COI. Individuals with a high COI were excluded from the Expert Panel unless they were able to reduce their level of COI. Expert Panel members who reduced the level of a high COI were then subject to the requirements, including recusals, associated with lower levels of COI.

Interactions related to a specific priority topic with a single biomedical entity were considered moderate COIs. Expert Panel members with a moderate COI related to any of the six priority topics were recused from participating in the writing, discussion, and voting on the recommendations or guideline section for that topic. This recusal process was implemented at the start of the Expert Panel's work, and the Expert Panel formally recognized these COIs as moderate after the release of the ACP recommendations. Resolution of a moderate COI resulted in reinstatement to full participation in all activities related to that topic. Any report of a previously unreported moderate COI resulted in recusal of the member from activities related to that topic. In addition, members who had no COI discussed the topic again and voted again on the associated recommendations. A low conflict of interest was defined as no more than two interactions with a biomedical entity not related to asthma or to the topics under discussion.

As new COIs arose during the guideline-development process, Expert Panel members reported these COIs to the Expert Panel chair, and the chair and the JACI editors reviewed these new COIs and developed a plan to manage them. All Expert Panel members were notified when a member reported a new COI. After the release of the ACP recommendations, Expert Panel members with any new COI were recused from the Expert Panel. All Expert Panel members agreed not to undertake any activities that could result in a new COI for 12 months after the guidelines were released.

GRADE Methodology

Overview

GRADE is an internationally accepted framework for determining the quality or certainty of evidence and the direction and strength of recommendations based on this evidence.[16,17] A guideline methodologist not involved in the development of the systematic reviews for this update provided training on GRADE methodology to the Expert Panel and ongoing support and consultation throughout the project. The Expert Panel used the GRADE approach to review the evidence, create evidence profiles for *critical and important outcomes*, develop EtD tables, and write recommendation statements.

Prioritization and Rating of Asthma Outcomes

The Expert Panel discussed asthma outcomes of potential interest and rated the relative importance of each outcome for clinical decision-making using the GRADE approach.[18] During this process, the Expert Panel reviewed the definitions of the outcomes in each of the systematic review reports. The outcomes deemed *critical* to assess for making recommendations across all topic areas were asthma exacerbations, asthma control, and asthma-related quality of life.

The Expert Panel assessed additional outcomes for specific key questions when these outcomes were relevant to the topic or when data for the three *critical* outcomes were not available. For example, in some instances, the systematic review reports identified limited or no adequate data on the effect of the interventions listed in the key questions on specific *critical* outcomes (e.g., asthma control). In such cases, the Expert Panel considered available data on a related outcome (e.g., asthma symptoms), even though validated outcome instruments were not used in studies or were not available. In this example, the Expert Panel confirmed asthma symptoms as an important outcome based on responses from the focus groups. The Expert Panel then used data on this important outcome to create the evidence profiles and EtD tables for the intervention, based on the available evidence.

After prioritizing the outcomes, the Expert Panel used established thresholds for determining significant improvement, also known as the minimally important difference (MID), for asthma control and asthma-related quality-of-life measures. These MID criteria are listed in Table I.b. For outcomes with no MID established in the literature, such as exacerbations, the Expert Panel reached consensus on clinically important differences that were based in part on a review of effect sizes in randomized controlled trials in the literature and on their judgments regarding the clinical relevance of a given change. In keeping with the recommendations from the Asthma Outcomes Workshop (2012),[10] treatment with systemic (oral and parenteral) corticosteroids, asthma-specific emergency department visits, and hospitalizations were included as core outcome measures for exacerbations. The Expert Panel also included studies that used composite measures of systemic corticosteroids, emergency department visits, and hospitalizations.[19]

Table I.b: Minimally Important Differences (MIDs) for Asthma-Control and Asthma-Related Quality-of-Life Measures[20-28]

Outcome Measure	Range (points)	Score Interpretation	MID
ASTHMA CONTROL			
Asthma Control Test (ACT)	5 to 25	Well controlled: ≥20 Not well controlled: ≤19	≥12 years: MID ≥3 points
Asthma Control Questionnaire-5 (ACQ-5) **Asthma Control Questionnaire-6** (ACQ-6)	0 to 6	Uncontrolled: ≥1.5 Well controlled: <0.75	≥18 years: MID ≥0.5 points
Asthma Control Questionnaire-7 (ACQ-7)	0 to 6	Uncontrolled: ≥1.5 Well-controlled: <0.75	≥6 years: MID ≥0.5 points

Outcome Measure	Range (points)	Score Interpretation	MID
ASTHMA-RELATED QUALITY OF LIFE			
Asthma Quality of Life Questionnaire (AQLQ) **Asthma Quality of Life Questionnaire Mini** (AQLQ-mini)	1 to 7	Severe impairment = 1 No impairment = 7	≥18 years: MID ≥0.5 points
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	1 to 7	Severe impairment = 1 No impairment = 7	7–17 years: MID ≥0.5 points
OTHER			
Rescue medication use (daytime or nighttime)	Continuous measure of puffs per unit of time	N/A	≥18 years: MID = –0.81 puffs/day

Evidence to Decision Framework

The EtD framework provides a systematic and transparent approach for moving from evidence to recommendations by guideline panels.[29] The topic teams developed EtD tables for each key question using the evidence in the systematic review reports and the GRADEpro Guideline Development Tool.[30] New articles found in the updated literature review were noted in the new evidence sections of the EtD tables, but their data were not incorporated into the pooled estimates. See Table I.c for the template used for EtD tables. The EtD tables provided a framework for the Expert Panel to use for assessing the evidence and providing rationales for their judgments on a range of factors that influenced the recommendations, as described in the next section, "Contextualization of Judgments."[31,32]

Table I.c: Evidence to Decision Table Template

Content Area	Question	Judgment (pick one)	Research evidence	Additional considerations
Desirable effects	How substantial are the desirable anticipated effects?	Trivial, small, moderate, large, varies, don't know		
Undesirable effects	How substantial are the undesirable anticipated effects?	Large, moderate, small, trivial, varies, don't know		
Certainty of evidence	What is the overall certainty of the evidence of the effects?	Very low, low, moderate, high, no included studies		

Content Area	Question	Judgment (pick one)	Research evidence	Additional considerations
Values	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability, possibly important uncertainty or variability, probably no important uncertainty or variability, no important uncertainty or variability		
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Favors the comparison, probably favors the comparison, does not favor either the intervention or the comparison, probably favors the intervention, favors the intervention, varies, don't know		
Acceptability	Is the intervention acceptable to key stakeholders?	No, probably no, probably yes, yes, varies, don't know		
Feasibility	Is the intervention feasible to implement?	No, probably no, probably yes, yes, varies, don't know		
Equity	What would be the impact on health equity?	Reduced, probably reduced, probably no impact, probably increased, increased, varies, don't know		

Contextualization of Judgments

The Expert Panel members reviewed the summary-of-findings tables in the AHRQ systematic review reports and recorded their judgments about the certainty of the evidence regarding each intervention. See Table I.d for explanations of the levels of certainty in the evidence. For each key question, the Expert Panel reviewed the EPCs' judgments about the risk of bias reported in the systematic review reports. The Expert Panel modified the judgments about the directness or indirectness of, consistency or inconsistency of, precision or imprecision of, and publication bias in the evidence when appropriate to reflect the panel's contextualized judgments about the certainty of the evidence in the context of clinical practice guidelines.[32] Footnotes in the EtD tables in Appendix B provide detailed explanations of these judgments. When the Expert Panel made a contextualized judgment for a specific outcome (and the opinion of the Expert Panel differed from the judgment of the EPC in the AHRQ systematic review report), the Expert Panel used the following words: "The Expert Panel rated this outcome down for…". Otherwise, the certainty of evidence and risk of bias ratings reflected the EPCs' judgments from the published systematic review reports, and the Expert Panel identified these ratings by statements that began with "The AHRQ systematic review report rated this outcome down for…"

Table I.d: Certainty of Evidence of Effects

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Each EtD table includes a summary of the pooled results from the evidence syntheses (in addition to results from any new studies) in relative and absolute terms. The tables also describe any assumptions or evidence on variability in patient values and preferences regarding the intervention; the overall certainty of the evidence; the intervention's net benefit based on the desirable and undesirable effects; and judgments about the resource requirements, acceptability, feasibility, and equity issues related to that intervention. The Expert Panel members made judgments within these domains and developed clinical recommendations based on the evidence summarized in the EtD tables. Discussions to make these judgments and develop the recommendations took place during online, telephone, and face-to-face meetings. For each recommendation, the Expert Panel indicated its direction (for or against the intervention) and strength, provided accompanying technical remarks and implementation considerations, and identified relevant evidence gaps.

Framing Recommendations and Coming to Consensus

In GRADE, each recommendation has a direction, meaning that the recommendation is either for or against the use of an intervention. Each recommendation is also either strong or conditional, as explained in Table I.e. *Strong* recommendations are those for which, in the judgment of the Expert Panel after it has reviewed all of the evidence and individual judgments, all or almost all people would choose the recommended course of action. *Conditional* recommendations are those for which, after reviewing all of the evidence and individual judgments, the Expert Panel believes that many informed people are likely to make different decisions about whether to take the recommended course of action. A conditional recommendation implies that engaging in a shared decision-making process is essential for individuals with asthma and their health care providers.[31-33]

Table I.e: Implications of Strong and Conditional Recommendations*

Implications	Strong recommendation	Conditional recommendation
For individuals with asthma	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individuals consistent with their values and preferences. Use shared decision-making. Decision aids may be useful in helping individuals make decisions consistent with their risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is documented.
For researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

*Strong recommendations are indicated by statements that lead with "We recommend," whereas conditional recommendations are indicated by statements that lead with "We conditionally recommend."

The Expert Panel drafted, discussed, and revised the recommendations multiple times before all eligible members (those who did not have a COI for the topic) voted on each recommendation. The Expert Panel achieved consensus when more than 90 percent of the Expert Panel members voted in favor of a recommendation. If less than 90 percent of members voted in favor of a recommendation, the relevant topic team continued to revise the recommendation until it achieved consensus approval according to these criteria.

Focus Groups with Individuals with Asthma and Their Caregivers

The NHLBI sponsored focus groups with individuals with asthma and their caregivers to:

- Identify the types of information and tools that individuals with asthma, their caregivers, and their health care providers would find most helpful in their ongoing efforts to effectively manage asthma and adhere to the new guidelines
- Ensure that the new asthma guidelines reflect the voices of individuals with asthma and their caregivers
- Identify potential barriers to uptake by individuals with asthma and their caregivers

- Using virtual data-collection methods (i.e., telephone and online platforms), the NHLBI conducted 11 in-depth interviews with health care providers who treat individuals with asthma and 10 online focus groups with English- and Spanish-speaking adults with asthma and adult caregivers of children with asthma with household incomes lower than $50,000 per year. In accordance with best practices, both the health care provider in-depth interviews and consumer focus group sessions lasted 75 minutes or less to minimize burden and facilitate engagement. Findings were analyzed using a notes- and transcript-based analysis process similar to that recommended by Krueger[34] and Patton.[35]

The focus groups provided insight into outcomes that individuals with asthma and their caregivers considered most important; factors that affected their treatment choices; preferences for medication type and dosing frequency; and opinions about immunotherapy, allergen reduction, and BT. The Expert Panel considered these insights when developing its recommendations and EtD tables.

Findings of Interviews and Focus Groups

Among both adults with asthma and caregivers of children with asthma, the most desired outcome was relief from symptoms that limit what people with asthma can do. In particular, participants valued symptom relief that would allow individuals with asthma to be more physically active. Caregivers also wanted to reduce the number of hospital visits for individuals with asthma, and Spanish-speaking caregivers sought control of nighttime symptoms. These individuals with asthma and caregiver preferences support the use of asthma symptom relief as an outcome measure when studies did not use validated outcome measurement tools.

Participants stated that cost and insurance coverage, safety, side effects, benefits, success rates, and asthma severity influenced their decisions about asthma treatment. Some participants were concerned that they might become dependent on or addicted to asthma medications (in particular, to pills), and participants with comorbidities expressed concern about drug interactions and contraindications, especially for oral medications.

Individuals with asthma indicated that they preferred inhaled medications over pills or liquids because they perceived inhaled medications to be easier to take or administer, faster acting, and more effective (because the medication is delivered directly to the site where it is needed). Individuals with asthma and caregivers also preferred taking one medication daily at most and viewed a need to take more than two to three medications a day as excessive. Caregivers were concerned about the administration of more medications or more frequent administration of medications to children while they are in school.

Taking medication on a set schedule instead of as needed drew mixed reactions. Perceived benefits of a set schedule included easier adherence, greater effectiveness, and a greater ability to prevent exacerbations (for those with severe asthma). In contrast, taking medication as needed was believed to offer flexibility and potentially reduce side effects. As-needed medications were also described as more appealing to those with mild to moderate asthma and to Spanish-speaking caregivers. Adults with asthma and caregivers were generally receptive to use of one inhaler to both treat asthma and prevent exacerbations, although they wondered whether medications could do both effectively.

Levels of awareness of immunotherapy were low to moderate in individuals with asthma and caregivers. Some stated that they would consider this type of treatment if it were shown to be effective; others remained skeptical about the value of immunotherapy because of concerns about associated pain, inconvenience, and side effects.

Many participants reported taking action to reduce allergens at home. Most participants said that they used mattress and pillow covers, removed curtains or mold, controlled pests and dust, and vacuumed floors regularly. Some participants who had pets said that the pets were outside most of the time or they vacuumed their floors frequently. Participants also reported keeping windows closed during pollen and wildfire season to reduce the level of allergens and irritants in their home. Very few stated that they would stop their current allergen reduction efforts even if these efforts were proven to be ineffective. Most participants wanted information on cost and level of effort involved to consider making a change.

Spanish-speaking adults with asthma were more receptive to BT than their English-speaking counterparts. However, most participants thought that the procedure was too risky and expressed concerns about the need for anesthesia, multiple hospital visits, and heating of muscle tissue as well as the treatment's impact on other health conditions. They wanted more information on the therapy's side effects, risks, complications, and success rates as well as how the procedure is done.

2020 Focused Updates to the 2007 Asthma Guidelines

After the Expert Panel reached consensus on the recommendations, each topic team drafted a narrative to provide further information on each recommendation. These narratives form the body of this report. Each topic narrative has the following sections:

- A brief background section that includes definitions of the terms used in the recommendations
- The key questions addressed
- The recommendations
- An implementation guidance section that explains the recommendation in greater detail and provides Expert Panel opinion about how to implement the recommendation in clinical practice
- A summary of the evidence
- The rationale for the recommendation
- A discussion of the evidence supporting the recommendation
- A list of topic-specific research gaps and questions

Differences (if any) between the new recommendations and the recommendations in EPR-3 are discussed in Appendix A.

The implementation guidance sections are for practicing clinicians, and they contain the following information:

- Clinician's summary (more detailed explanation of the recommendation)
- Population most likely to benefit from the recommendation
- Any populations to which the recommendation does not apply
- Topic-specific considerations
- Issues that clinicians should discuss with their patients as part of the shared decision-making process.

Review and Public Comment

The NAEPPCC reviewed an initial draft report. The NHLBI subsequently made the draft report available for public review and comment from December 2, 2019, to January 17, 2020. Interested stakeholders—including health professionals; representatives of the scientific community, academic institutions, the private sector, professional societies, advocacy groups, and patient communities; and other interested members of the public—were invited to submit comments. The Expert Panel received and reviewed approximately 500 comments from almost 100 individuals and organizations, and the panel used this input to revise the draft report.

One or more individuals and organizational representatives who submitted public comments mentioned almost all of the emerging topics. Of the 11 emerging topics (see list toward the beginning of Section I of this report), biologic agents received the most attention. The first biologic agent for asthma received approval from the U.S. Food and Drug Administration in 2003, but the second biologic agent did not receive approval until November 2015. Between November 2015 and November 2017, four biologic agents received approval, but several others were not shown to be effective in clinical trials. Thus, at the time that the priority topics and key questions were developed, the only biologic agent available for use in the United States was omalizumab, which EPR-3 had addressed. The NHLBAC Asthma Expert Working Group did not believe that this single available biologic agent warranted inclusion in the update and included biologic agents as an emerging topic.

Limitations and Research Gaps

The Expert Panel identified several limitations in the process it used to identify topics and develop recommendations, including:

- A better mechanism is needed to identify topics that need updating and to decrease the time between updates.
- The process would benefit from a discussion and development of a plan about how to tailor guideline recommendations in the emerging era of personalized medicine.
- Expanding engagement with professional societies might benefit both the development and the implementation of new recommendations.

The panel also identified several overarching research gaps listed below. Research gaps that are specific to individual topics are listed at the end of each topic section.

- Research studies need to use the core outcome measures identified in the 2012 Asthma Outcomes Workshop.[10] Federal agencies that contributed to the 2012 Asthma Outcomes Workshop report should require the studies they fund to measure outcomes as recommended in that report. Because new information on asthma outcomes is now available, the workshop report should be reexamined to determine whether it needs to be revised.
- The clinical relevance of changes in outcome measures should be formally established to provide MIDs for all asthma outcomes (e.g., exacerbations and asthma symptoms) and the cutoffs for tests (e.g., FeNO). Clinical relevance should be established using a wide range of stakeholder input, especially from individuals with asthma, who should also be included as members of the Expert Panel.
- Updates are needed to the definitions of asthma severity that incorporate asthma phenotypes and endotypes. The definitions of low-, medium-, and high-dose inhaled corticosteroids also need to be updated.
- Biologically appropriate subpopulations with asthma should be established and standardized. Although the populations of interest for the focused updates were defined for the systematic reviews, the characterizations of study participants did not reflect current understanding of relevant phenotypes and endotypes (e.g., based on asthma severity, allergen-specific sensitization, or airway inflammatory type).
- Standard reporting of results stratified by race and ethnicity as well as by age groups (0–4 years, 5–11 years, and 12 years and older) is needed to combine results across studies.

- The vast majority of studies used to inform the guidelines were designed as efficacy studies,[36] which evaluate treatment effects in relatively homogeneous populations and conditions in which fidelity to study protocols is actively promoted. Applicability to real-world clinical and community contexts requires studies with comparative effectiveness designs. Such research would benefit from the use of validated outcome measures and definitions of biologically appropriate subpopulations.
- Studies need to use measures and outcomes that are important to individuals with asthma. GRADE methodology gives highest priority to patient-centered outcomes. However, the studies that the Expert Panel used to develop the recommendations often did not measure outcomes that are most relevant or important to individuals with asthma. Research is needed to understand how preferred outcomes vary by race or ethnicity, asthma severity, age (e.g., children or older adults), and socioeconomic status.
- All measures and outcomes relevant to making judgments need to be included in the systematic reviews. For example, although cost-effectiveness data are available for some asthma interventions, the systematic review reports used for the updates did not include these data. Moreover, data regarding the safety of all interventions should be explicitly reported in publications on clinical trials.

Recommendations

In Table I.f, all of the Expert Panel's recommendations are grouped by the six priority topics. Please refer to the topic-specific sections in this report for full discussions of each recommendation, including implementation guidance and a clinician's summary.

Table I.f: Expert Panel Recommendations

Topic	Recommendation number*	Recommendation	Strength of recommendation†	Certainty of evidence‡***
Fractional exhaled nitric oxide (FeNO)	1	In individuals ages 5 years and older for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed, the Expert Panel conditionally recommends the addition of FeNO measurement as an adjunct to the evaluation process.	Conditional	Moderate
	2	In individuals ages 5 years and older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, the Expert Panel conditionally recommends the addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments.	Conditional	Low
	3	In individuals ages 5 years and older with asthma, the Expert Panel recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity. If used, it should be as part of an ongoing monitoring and management strategy.	Strong	Low
	4	In children ages 0–4 years with recurrent wheezing, the Expert Panel recommends against FeNO measurement to predict the future development of asthma.	Strong	Low

Topic	Recommendation number*	Recommendation	Strength of recommendation†	Certainty of evidence‡***
Allergen mitigation	5	In individuals with asthma who do not have sensitization to specific indoor allergens or who do not have symptoms related to exposure to specific indoor allergens, the Expert Panel conditionally recommends against allergen mitigation interventions as part of routine asthma management.	Conditional	Low
	6	In individuals with asthma who have symptoms related to exposure to identified indoor allergens, confirmed by history taking or allergy testing, the Expert Panel conditionally recommends a multicomponent allergen-specific mitigation intervention	Conditional	Low
	7	In individuals with asthma who have sensitization or symptoms related to exposure to pests (cockroach and rodent), the Expert Panel conditionally recommends the use of integrated pest management alone, or as part of a multicomponent allergen-specific mitigation intervention.	Conditional	Low
	8	In individuals with asthma who have sensitization or symptoms related to exposure to dust mites, the Expert Panel conditionally recommends impermeable pillow/mattress covers only as part of a multicomponent allergen mitigation intervention, not as a single-component intervention.	Conditional	Moderate

Topic	Recommendation number*	Recommendation	Strength of recommendation†	Certainty of evidence‡***
Inhaled Corticosteroids (ICS)	9	In children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, the Expert Panel conditionally recommends starting a short course of daily ICS at the onset of a respiratory tract infection with as-needed SABA for quick-relief therapy compared to as-needed SABA for quick-relief therapy only.	Conditional	High
	10	In individuals ages 12 years and older with mild persistent asthma, the Expert Panel conditionally recommends either daily low-dose ICS and as-needed SABA for quick-relief therapy or as-needed ICS and SABA used concomitantly.	Conditional	Moderate
	11	In individuals ages 4 years and older with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, the Expert Panel conditionally recommends against a short-term increase in the ICS dose for increased symptoms or decreased peak flow.	Conditional	Low
	12	In individuals ages 4 years and older with moderate to severe persistent asthma, the Expert Panel recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to either: ▪ Higher-dose ICS as daily controller therapy and SABA for quick-relief therapy, or ▪ Same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.	Strong	High (ages ≥12 years) Moderate (ages 4-11 years)

Topic	Recommendation number*	Recommendation	Strength of recommendation†	Certainty of evidence‡***
Inhaled Corticosteroids (ICS)	13	In individuals ages 12 years and older with moderate to severe persistent asthma, the Expert Panel conditionally recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to higher-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.	Conditional	High
Long-acting muscarinic antagonist (LAMA)	14	In individuals ages 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends against adding LAMA to ICS compared to adding LABA to ICS.	Conditional	Moderate
	15	If LABA is not used, in individuals ages 12 years and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS controller therapy compared to continuing the same dose of ICS alone.	Conditional	Moderate
	16	In individuals ages 12 and older with uncontrolled persistent asthma, the Expert Panel conditionally recommends adding LAMA to ICS-LABA compared to continuing the same dose of ICS-LABA.	Conditional	Moderate

Topic	Recommendation number*	Recommendation	Strength of recommendation†	Certainty of evidence‡***
Immunotherapy	17	In individuals ages 5 years and older with mild to moderate allergic asthma, the Expert Panel conditionally recommends the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in those individuals whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy.	Conditional	Moderate
	18	In individuals with persistent allergic asthma, the Expert Panel conditionally recommends against the use of sublingual immunotherapy in asthma treatment.	Conditional	Moderate
Bronchial Thermoplasty (BT)	19	In individuals ages 18 years and older with persistent asthma, the Expert Panel conditionally recommends against bronchial thermoplasty. Individuals ages 18 years and older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long-term side effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty.	Conditional	Low

*Recommendations are numbered throughout the document for ease of reference.
†See Table I.e on page 12 for definitions of the strength of recommendations.
‡See Table I.d on page 11 for definitions of the levels of certainty of evidence of effects.

Abbreviations: LABA, long-acting beta$_2$-agonist; SABA, short-acting beta$_2$-agonist

Integration of the New Recommendations into Asthma Care

The Expert Panel that produced this 2020 asthma guideline update was asked to address specific questions about six priority topics rather than revise all of EPR-3. The Expert Panel, however, recognized the need to integrate the new evidence-based recommendations into a comprehensive approach to asthma care using the EPR-3 step diagrams.

Stepwise Approach for Managing Asthma

In preparing the step diagrams (Figures I.b, I.c, and I.d), the Expert Panel used some of the definitions and assumptions from EPR-3. The step diagrams that follow this section retain the EPR-3 recommendations that the Expert Panel did not address in the current report. The Expert Panel encourages readers to review the footnotes in the step diagrams because they offer important information about the use of these diagrams.

The following conventions apply to Figures I.b, I.c, and I.d:

- Each figure applies to the care of individuals with asthma in one age group.
  - Figure I.b applies only to ages 0–4 years.
  - Figure I.c applies only to ages 5–11 years.
  - Figure I.d applies only to ages 12 years and older.
- Clinicians decide which step of care is appropriate depending on whether the individual is newly diagnosed (i.e., is treatment naïve) or whether the clinician is adjusting the individual's therapy to achieve asthma control.
  - For newly diagnosed or treatment-naïve individuals, clinicians should first choose the appropriate step diagram for the person's age and then consider both the individual's level of asthma impairment and risk when selecting the initial step and treatment.
  - Within a given step, the preferred options are the best management choices supported by the evidence that the Expert Panel reviewed. When the available evidence is insufficient or does not change a previous recommendation, the step diagrams list preferred options from the EPR-3 step diagrams.
  - Within a given step, alternative option(s) are management strategies that are less effective or have more limited evidence than the preferred options. Clinicians and patients may choose the alternative treatments if individuals with asthma are currently receiving this therapy and their asthma is under control, if the preferred treatments are not available or too costly, or if the individuals with asthma prefer an alternative treatment.
  - Preferred and alternative treatments within a step category are listed alphabetically unless the Expert Panel has established a rank order of preference for the preferred or alternative treatments. A lack of rank order is indicated by "or" between treatment options.

- In the stepwise approach to therapy for asthma, the clinician escalates treatment as needed (by moving to a higher step) or, if possible, deescalates treatment (by moving to a lower step) once the individual's asthma is well controlled for at least 3 consecutive months.
  - For individuals with persistent asthma (i.e., who require treatment at step 2 or above), clinicians should be guided by the current step of treatment and the individual's response to therapy (in terms of both asthma control and adverse effects) both currently and in the past to decide whether to step up, step down, or continue the current therapy.
  - For individuals with persistent asthma who are using an alternative treatment and have an unsatisfactory or inadequate response to that therapy, the Expert Panel suggests replacing the alternative treatment with the preferred treatment within the same step before stepping up therapy.
- The Expert Panel did not add management options that the panel recommends against, or for which the evidence is insufficient to determine harms and benefits, to the step diagrams. Instead, these options are listed in Table I.f.
- The guidance provided in the step diagrams is meant to assist and not replace the clinical decision-making required for individual patient management[12] and the input from individuals with asthma about their preferences.

Figure I.b: Stepwise Approach for Management of Asthma in Individuals Ages 0–4 Years

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 0–4 Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA and At the start of RTI: Add short course daily ICS▲	Daily low-dose ICS and PRN SABA	Daily medium-dose ICS and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily montelukast* or Cromolyn,* and PRN SABA		Daily medium-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA
			For children age 4 years only, see Step 3 and Step 4 on Management of Persistent Asthma in Individuals Ages 5–11 Years diagram.			

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required. Consider consultation at Step 2.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist; RTI, respiratory tract infection; PRN, as needed

▲ Updated based on the 2020 guidelines.

* Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020.

NOTES FOR INDIVIDUALS AGES 0–4 YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment. • Consider short course of oral systemic corticosteroid if exacerbation is severe or individual has history of previous severe exacerbations.

Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲

Notes	• If clear benefit is not observed within 4–6 weeks and the medication technique and adherence are satisfactory, the clinician should consider adjusting therapy or alternative diagnoses.

Abbreviations	EIB, exercise-induced bronchoconstriction; SABA, inhaled short-acting beta$_2$-agonist. ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.

Figure I.c: Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider Omalizumab**▲	

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** Omalizumab is the only asthma biologic currently FDA-approved for this age range.

NOTES FOR INDIVIDUALS AGES 5–11 YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • In Steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 8 puffs (36 mcg).▲ • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.
Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲
Notes	• The terms ICS-LABA and ICS-formoterol indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler. • Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol. • In individuals ages 5–11 years with persistent allergic asthma in which there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, FeNO measurement is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessment.
Abbreviations	EIB (exercise-induced bronchoconstriction); FeNO (fractional exhaled nitric oxide); ICS (inhaled corticosteroid); LABA (long-acting beta$_2$-agonist); SABA (inhaled short-acting beta$_2$-agonist). ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

NOTES FOR INDIVIDUALS AGES 12+ YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on the severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • In steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 12 puffs (54 mcg).▲ • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.
Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲
Notes	• The terms ICS-LABA and ICS-formoterol indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler. • Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol. • In individuals ages 12 years and older with persistent allergic asthma in which there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, FeNO measurement is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessment. • Bronchial thermoplasty was evaluated in Step 6. The outcome was a conditional recommendation against the therapy.
Abbreviations	EIB, exercise-induced bronchoconstriction; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist. ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.

SECTION II

Recommendations on the Use of Fractional Exhaled Nitric Oxide Testing in the Diagnosis and Management of Asthma

Background

Nitric oxide can be measured in exhaled breath and can serve as a measure of the level of airway inflammation. In individuals with asthma, fractional exhaled nitric oxide (FeNO) may be a useful indicator of type 2 (T2) bronchial or eosinophilic inflammation in the airway. FeNO testing requires an expiratory maneuver into a device designed for this purpose.

The Expert Panel addressed key questions on the utility of FeNO measurement for asthma diagnosis, management, and prognosis. In this section, the panel discusses factors that confound FeNO measurement or the interpretation of FeNO test results in the context of the key questions. The evidence in all of these areas reveals important limitations that affect the strength of the recommendations and limit the ability to determine the optimal strategies for FeNO measurement. A discussion of the equipment used to measure FeNO and how to perform the test is beyond the scope of this update.

Definitions of Terms Used in this Section

Children and adults have allergic asthma if they become symptomatic after acute exposure to something to which they are allergic (e.g., a pet) or during a specific season of the year (e.g., in the spring, due to tree pollen, or in the fall, due to ragweed pollen).

“Recurrent wheezing” is defined as clinically significant periods of bronchial or respiratory tract wheezing that is reversible or that is consistent with the clinical picture of bronchospasm.

Question 2.1

What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 years and older?

Recommendation 1: In individuals ages 5 years and older for whom the diagnosis of asthma is uncertain using history, clinical findings, clinical course, and spirometry, including bronchodilator responsiveness testing, or in whom spirometry cannot be performed, the Expert Panel conditionally recommends the addition of FeNO measurement as an adjunct to the evaluation process.

Conditional recommendation, moderate certainty of evidence

Implementation Guidance

CLINICIAN'S SUMMARY:

The role of an increased level of FeNO in the diagnosis of asthma is still evolving, and no definitive test exists for diagnosing asthma. FeNO measurement may support a diagnosis of asthma in individuals for whom the diagnosis is uncertain even after a complete history, physical examination, and spirometry testing including bronchodilator responsiveness. Recognition of allergen sensitivity is extremely important for interpreting FeNO levels. Allergic rhinitis and atopy, which can be present in individuals with and without asthma, are associated with increased FeNO levels, and taking these factors into consideration is critical for accurately interpreting FeNO test results.

On the basis of current data on FeNO measurement in clinical settings, FeNO testing has a supportive role in evaluation when the diagnosis of asthma is uncertain. The Expert Panel makes the following suggestions for use of FeNO testing in asthma diagnosis:

- Individuals in whom a diagnosis of asthma is being considered who may benefit from FeNO measurement as part of the evaluation process include:
  - Those ages 5 years and older who have an uncertain diagnosis of asthma
  - Those in whom spirometry testing cannot be performed accurately
- Because the data on the diagnostic accuracy of FeNO measurement in children younger than 4 years are not conclusive, FeNO measurement in this age group should not be used.
- FeNO test results should not be used alone to diagnose asthma. FeNO measurements can serve as an adjunct test that may aid in diagnosing asthma in the appropriate setting. After clinicians consider other conditions that may influence FeNO levels, they should perform the test when the results of a thorough clinical assessment, including other appropriate tests, are inconclusive.

- Clinicians should use the cutoff levels or ranges listed in Table II for FeNO measurement when evaluating persons for asthma. The likelihood that individuals ages 5 years and older have asthma increases by 2.8 to 7.0 times when the FeNO test result is high. Clinicians who use FeNO testing for asthma diagnosis should keep the following considerations in mind:
  - FeNO levels of less than 25 ppb (or less than 20 ppb in children ages 5–12 years) are inconsistent with T2 inflammation and suggest a diagnosis other than asthma (or that the individual has asthma but their T2 inflammation has been managed with corticosteroids or they have non-T2 inflammation or noneosinophilic asthma).
  - FeNO levels greater than 50 ppb (or greater than 35 ppb in children ages 5–12 years) are consistent with elevated T2 inflammation and support a diagnosis of asthma. Individuals who have T2 inflammation are more likely to respond to corticosteroid treatment.
  - FeNO levels of 25 ppb to 50 ppb (or 20–35 ppb in children ages 5–12 years) provide little information on the diagnosis of asthma and should be interpreted with caution and attention to the clinical context.
  - The specificity and sensitivity of the FeNO testing process depend on the clinical situation. However, in corticosteroid-naïve individuals with asthma, FeNO measurement is most accurate for ruling out the diagnosis of asthma when the result is less than 20 ppb. In this situation, the test has a sensitivity of 0.79, a specificity of 0.77, and a diagnostic odds ratio (OR) of 12.25.
  - Inhaled corticosteroid treatment should not be withheld solely based on low FeNO levels.

Table II: Interpretations of FeNO Test Results for Asthma Diagnosis in Nonsmoking Individuals Not Taking Corticosteroids*

FeNO Level		
<25 ppb (<20 in children ages 5–12)	**25–50 ppb (20–35 in children ages 5–12)**	**>50 ppb (>35 in children ages 5–12)**
▪ Recent or current corticosteroid use ▪ Alternative diagnoses ▪ Phenotype less likely to benefit from ICS ▪ Noneosinophilic asthma ▪ COPD ▪ Bronchiectasis ▪ CF ▪ Vocal cord dysfunction ▪ Rhinosinusitis ▪ Smoking ▪ Obesity	▪ Evaluate in clinical context ▪ Consider other diagnoses ▪ Consider other factors influencing result ▪ Eosinophilic asthma less likely	▪ Eosinophilic airways inflammation likely ▪ Phenotype more likely to respond to ICS ▪ Allergic asthma ▪ Eosinophilic bronchitis

*Reprinted with permission of the American Thoracic Society, ©2019 American Thoracic Society. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: Interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J RespirCrit Care Med.* 2011 Sep 1;184(5):602-615. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Abbreviations: CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; ppb, parts per billion.

- FeNO measurements should be performed by appropriately trained personnel who have extensive experience in interpreting the result or who consult experienced clinicians who can interpret the findings accurately. FeNO testing can be performed in primary or specialty care settings. However, the costs of testing (i.e., for equipment and expendable supplies) may prohibit the test's adoption in the primary care office setting. Cost and the need for reproducible maneuvers will need to be addressed before home testing can become feasible.
- **What clinicians should discuss with their patients and families:** Clinicians should share the following information about FeNO testing with individuals suspected of having asthma and caregivers:
  - The FeNO measurement process is safe for almost everyone.
  - FeNO testing may be helpful in determining whether an individual has asthma, but it cannot be used to diagnose asthma.
  - Clinicians should inform individuals with asthma who have conditions or behaviors (such as smoking) that could affect the interpretation of the FeNO test results that these issues could limit the accuracy of diagnostic attempts.

- FeNO test results cannot be used in isolation. Their interpretation must take into account other clinical factors and traditional measures.
- The evidence favors the use of FeNO measurement as an adjunct to other diagnostic methods (including a structured history, clinical findings, and pulmonary function testing) when the results from these other measures are not conclusive.
- Decisions about treatment with an inhaled corticosteroid (ICS) are not dependent on FeNO measurements, but such measurements may help direct stepwise therapeutic choices.

Summary of the Evidence

No randomized controlled trials (RCTs) could be found to address Question 2.1 (see Appendix B evidence to decision [EtD] Table I).

More than 50 studies have been conducted, and some of these studies included healthy and symptomatic individuals, smokers and nonsmokers, atopic and nonatopic individuals, and individuals with and without a prior diagnosis of asthma. The protocols for diagnostic FeNO assessments varied, and conclusions about the optimal testing protocol remain uncertain.

Based on the Expert Panel's interpretation of the literature and the systematic review report findings, the overall certainty of evidence for this recommendation is moderate. The Expert Panel considers implementation of the recommendation in a broad population to be appropriate based on the diversity of the populations included in the systematic review report. The imprecision in the studies on the utility of FeNO measurement in asthma diagnosis is notable.

Rationale and Discussion

In the Expert Panel's opinion, an additional tool to aid in diagnosing asthma could be beneficial, especially when that tool may help identify specific asthma phenotypes. The Expert Panel considered many facets of harm, risk, opportunity, and benefits in making its recommendation.

The acceptability of FeNO measurement to individuals with a potential diagnosis of asthma is likely to be high, given that the test involves minimal effort and does not incur discomfort or side effects. Publications on studies that used FeNO testing did not report any overt harms. The Expert Panel noted that most studies conducted FeNO measurements only in specialty care research settings, and few data are available on the use of FeNO measurement in primary care settings. As with many innovations, the cost of FeNO equipment and testing may limit its broader use. These barriers to broader dissemination could have a negative impact on the availability of FeNO testing and lead to less equitable care for populations with limited resources.

Questions 2.2 and 2.3

- What is the clinical utility of FeNO measurements to select medication options (including corticosteroids) for individuals ages 5 years and older?
- What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 years and older?

Recommendation 2: In individuals ages 5 years and older with persistent allergic asthma, for whom there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, the Expert Panel conditionally recommends the addition of FeNO measurement as part of an ongoing asthma monitoring and management strategy that includes frequent assessments.

Conditional recommendation, low certainty of evidence

Implementation Guidance

Clinician's Summary:

This recommendation is specific to using FeNO levels when selecting therapy for individuals with asthma and when monitoring the response to and adjusting the dosage of anti-inflammatory therapies. This recommendation does not apply to individuals taking biologic agents, with the exception of omalizumab, because the systematic review literature searches conducted until October 2018 did not include data on biologic agents other than omalizumab. Clinicians must interpret FeNO levels in conjunction with other clinical data because these levels are affected by comorbid conditions, including allergic rhinitis and atopy. The weight of the evidence suggests that when used as part of an asthma management strategy, FeNO monitoring is effective in preventing exacerbations only when used frequently (such as every 2 to 3 months), but even frequent monitoring does not improve asthma control or quality of life in individuals with asthma.

The Expert Panel offers the following suggestions on how to use FeNO testing to monitor asthma:

- Individuals for whom FeNO testing may be useful to monitor asthma include:
  - Individuals ages 5 years and older with uncontrolled persistent asthma who are currently taking an ICS or an ICS with a long-acting $beta_2$-agonist, montelukast, or omalizumab
  - Individuals whose symptoms indicate that they might require additional anti-inflammatory therapy
  - Individuals with atopy, especially children
  - Individuals with asthma being treated by providers who agree that frequent (every 2 to 3 months) assessments of asthma control over the course of a year are warranted
- FeNO levels must be interpreted in conjunction with other clinical data. Current evidence suggests that FeNO can prevent exacerbations only when testing is used frequently (e.g., every 2 to 3 months). Cutpoints for adjusting therapy to reduce the risk of exacerbation have not been established.
- The Expert Panel does not recommend using FeNO testing to assess adherence to treatment (mostly for ICS) because the strength of this evidence is low. Moreover, although FeNO levels were associated with adherence to ICS as measured by electronic or dose counters in two observational studies[37,38] and one randomized controlled trial (RCT)[39] in 1,035 children and adolescents, no studies have evaluated FeNO monitoring to assess adherence in adults.

- FeNO levels are not well correlated with other asthma outcomes (e.g., symptoms or control measured by such tools as the Asthma Control Test [ACT] or Asthma Control Questionnaire [ACQ], prior or subsequent exacerbations, or exacerbation severity; see Recommendation 3). Therefore, clinicians should not use FeNO measurement as a substitute for these measures or in isolation. Rather, FeNO testing is best used as part of an ongoing asthma monitoring and management strategy that includes frequent assessments.
- **What clinicians should discuss with their patients and families:** The Expert Panel suggests that clinicians consider conveying the following information to their patients with asthma as part of shared decision-making:
  - FeNO measurement is safe for almost everyone.
  - FeNO-based asthma monitoring and management strategies are associated with significant reductions in exacerbation frequency, but not with improvements in control (based on ACT or ACQ results) or on quality of life measures.
  - To undergo FeNO testing, individuals with asthma might need to be referred to a specialty clinic.
  - FeNO measurements are used in addition to other evaluations of asthma control, such as lung function testing, symptom assessments, and questions about medication adherence.
  - FeNO levels may be affected by multiple conditions in addition to asthma.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life). The summary of evidence for Recommendation 2 can be found in Appendix B (EtD Table II).

In the Expert Panel's judgment, the benefit of FeNO monitoring is moderate. FeNO testing to monitor responses to asthma anti-inflammatory therapies was associated with a meaningful decrease in exacerbations, whereas the average benefit of FeNO monitoring for asthma control and quality of life did not achieve the minimally important difference (MID) (see EtD Table II). The certainty of evidence (for ACT, Pediatric Asthma Quality of Life Questionnaire, or Asthma Quality of Life Questionnaire) is low. The strategies for adjusting anti-inflammatory therapies using FeNO test results in conjunction with other assessments varied widely.[39-53] For this reason, no evidence-based FeNO cutpoints are available for choosing, monitoring, or adjusting anti-inflammatory therapies, and the Expert Panel has not provided an algorithm to use for this purpose. Most algorithms that have been used in studies involved strict protocols and may not be relevant to typical clinical practices.

The certainty of evidence for the effect of FeNO monitoring on exacerbations depends on the definition of an asthma exacerbation. For exacerbations that were defined in terms of a composite endpoint, the certainty of evidence is high. The composite exacerbation endpoint used in these studies was defined as any of the following: unscheduled visits to the provider's office, emergency department visits, hospitalizations, oral corticosteroid use, reductions in forced expiratory volume in 1 second or in peak expiratory flow, symptom-associated lung function decline, or Global Initiative for Asthma guideline definitions. The studies that compared an asthma management strategy that includes FeNO monitoring to one that does not include 6 RCTs in 1,536 adults (OR, 0.62; 95% confidence interval [CI], 0.45 to 0.86) and 7 RCTs in 733 children (OR, 0.50; 95% CI, 0.31 to 0.82). Strategies that include FeNO monitoring in adults result in an absolute risk reduction of 71 exacerbations per 1,000 individuals with asthma (range of 108 to 25 fewer exacerbations). FeNO monitoring is also associated with 116 fewer exacerbations per 1,000 children with asthma. When only exacerbations that result in oral corticosteroid use are used (based on 10 RCTs in 1,664 adults and children), the certainty of evidence is moderate (OR, 0.67; 95% CI, 0.51 to 0.90). The absolute risk difference is 67 fewer exacerbations per

1,000 individuals with asthma (range of 104 to 19 fewer exacerbations). For exacerbations that result in hospitalization (9 RCTs in 1,598 adults and children), the certainty of evidence is low (OR, 0.70; 95% CI, 0.32 to 1.55). The absolute risk difference is 11 fewer exacerbations per 1,000 individuals with asthma (range of 25 fewer to 19 more exacerbations).

The certainty of evidence is low for FeNO monitoring to exert a change of at least the established MID using the ACT (MID, 3), Pediatric Asthma Quality of Life Questionnaire (MID, 0.5), or Asthma Quality of Life Questionnaire (MID, 0.5). For each of these outcomes, the mean difference in scores between groups with and without FeNO monitoring was less than 0.1.

It is not known whether the recommendation applies to children who do not have allergic asthma because atopy (defined based on a positive skin prick test or elevated aero-allergen-specific immunoglobulin E) and allergic asthma were inclusion criteria in most of the pediatric studies, or allergic asthma was highly prevalent in the study populations.[39,41,42,45-48,53-55] For the studies of adults, the presence of atopy was less consistently reported[43,52,56] or was assessed as part of the study.[40,44,49-51,57] Therefore, the evidence supporting this recommendation comes from mixed populations of allergic and nonallergic adults.

Studies evaluating the use of FeNO to help select or monitor responses to biologic agents, with the exception of omalizumab, were not available for assessment. Therefore, whether this recommendation applies to other biologic agents is not known.

Rationale and Discussion

In making this recommendation, the Expert Panel considered the desirable and undesirable effects of FeNO monitoring, including the acceptability of this testing to both individuals with asthma and their providers, the feasibility of testing, and the impact of the use of FeNO testing to monitor asthma on health equity. Potential benefits of FeNO testing include reducing exacerbations, which is a *critical* outcome from both the patient and provider perspectives. The undesirable direct effects of FeNO testing are expected to be minimal. However, the Expert Panel had concerns about the impact of FeNO testing for asthma monitoring on accessibility and equity, as noted below.

FeNO levels have been shown to be responsive to changes in anti-inflammatory medications, including inhaled corticosteroids, montelukast, and omalizumab. The Expert Panel did not review the effects on FeNO levels of newly available anti-inflammatory biologic therapies for this update.

In the Expert Panel's judgment, individual preferences and values have an important role in the decision to use FeNO monitoring. This monitoring can affect quality of life and exacerbation frequency, and different individuals are likely to place different values on these effects. In addition, the burden (cost, time for appointments, and availability of testing) of frequent monitoring will likely influence an individual's willingness to undergo regular testing. Therefore, a therapeutic monitoring plan that includes frequent FeNO testing requires discussion and agreement between the individual with asthma and the clinician.

The Expert Panel was concerned that if FeNO testing is not widely available and its use is restricted by insurance coverage policies, some individuals with asthma might not have the benefit of exacerbation reduction using FeNO-based monitoring and management algorithms. As a result, disparities in asthma outcomes would widen. Most of the FeNO monitoring studies with cost-effectiveness data were conducted outside the United States[44,58-61] and were therefore of limited value for this update. The Expert Panel recommends cost-effectiveness analyses conducted in the United States.

Question 2.4

What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma aged 5 years and older?

Recommendation 3: In individuals aged 5 years and older with asthma, the Expert Panel recommends against the use of FeNO measurements in isolation to assess asthma control, predict future exacerbations, or assess exacerbation severity. FeNO should only be used as part of an ongoing monitoring and management strategy.

Strong recommendation, low certainty of evidence

Implementation Guidance

Clinician's Summary:

The Expert Panel does not recommend FeNO testing on its own to assess asthma control, predict a future asthma exacerbation, or assess the severity of an exacerbation. FeNO levels are not well correlated with standard measures of asthma symptoms or control, such as the ACT, ACQ, prior or subsequent exacerbations, or exacerbation severity. Therefore, FeNO testing is not a substitute for standard measures and should not be used in isolation to monitor disease activity. FeNO measurement, however, may be used in conjunction with an individual's history, clinical findings, and spirometry as part of an ongoing asthma monitoring and management strategy, which includes frequent assessments as described in recommendation 2.

- The Expert Panel recommends against the use of isolated FeNO measurement for asthma management and monitoring.
- FeNO measurement should only be used as a part of an ongoing monitoring and management strategy to predict future exacerbations and assess exacerbation severity.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life).

The Expert Panel considered the use of FeNO measurement in adults ages 18 years or older and children ages 5–18 years to monitor current asthma control, subsequent and prior exacerbations, and the severity of an ongoing exacerbation. The evidence for these issues comes primarily from correlational studies.

Among adults, FeNO levels are weakly associated with asthma control as measured by the ACT and ACQ.[62-65] This association is even weaker among individuals who smoke, are pregnant, or are taking an ICS. The association between FeNO levels and prior or subsequent exacerbations is mixed—depending on the study, this association is strong[66] or weak,[67] or no such association[62] exists. Among children and adolescents ages 5–18 years, the results are also mixed. For example, two studies showed an association between recent symptoms or uncontrolled asthma and elevated FeNO levels.[68,69] However, another

study showed that FeNO levels did not correlate with nasal or asthma symptoms.[70]

The evidence on the utility of FeNO testing to predict exacerbations is inconclusive. These studies assessed different populations and used FeNO levels alone as predictors or as part of a strategy that included other tests. For example, two studies showed that FeNO levels were moderate predictors of exacerbations.[42,71] In contrast, other studies showed that FeNO levels, in conjunction with inflammatory markers and clinical characteristics, did not predict exacerbations[72] and that FeNO levels did not predict future exacerbations among high-risk urban children from minority populations.[73]

Among children and adults, FeNO levels did not correlate with exacerbation severity.[74,75] FeNO testing was also difficult to perform in children in the acute setting, the results did not correlate with other measures of acute severity,[76] and the results were poorly reproducible for individual patients during an exacerbation.[77]

Rationale and Discussion

Based on the evidence summarized above, the Expert Panel recommends against the use of FeNO measurement to assess asthma control, predict future exacerbations, or assess exacerbation severity unless these measurements are used as part of an ongoing asthma monitoring and management strategy as described in Recommendation 2. Further research is needed to assess the use of FeNO as a marker for medication adherence, as well as its impact on asthma outcomes, acceptability, and cost effectiveness.

Question 2.5

In children ages 0–4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at ages 5 and above?

Recommendation 4: In children ages 0–4 years with recurrent wheezing, the Expert Panel recommends against FeNO measurement to predict the future development of asthma.

Strong recommendation, low certainty of evidence

Implementation Guidance

Clinician's Summary:

In children ages 4 years and younger who have recurrent episodes of wheezing, FeNO measurement does not reliably predict the future development of asthma. FeNO test results in this population should be interpreted with caution until more data are available. The Expert Panel recommends against using FeNO testing to predict future development of asthma in this age group until additional research and clinical practice determinations are available.

Summary of the Evidence

The summary of evidence for Recommendation 4 can be found in EtD Table III in Appendix B.

Ten studies addressed the ability of FeNO measures in children younger than 5 years to predict the subsequent development of asthma in children ages 5 years and older.[78-87] None of these studies were RCTs; seven studies were nonrandomized longitudinal studies and three were cross-sectional studies. Only four studies investigated the use of FeNO measures to predict the diagnosis of asthma (and not wheezing or Asthma Predictive Index [API] score). In one study in children,[86] a FeNO level indicating an increased risk of asthma had a positive predictive value of 58.0% on a composite measure of wheezing, diagnosis of asthma, or use of an ICS at age 7, whereas the negative predictive value was 78.2%. This result was similar to that for the classical API score without the use of FeNO levels. Therefore, although FeNO levels appear to reflect eosinophilic bronchial inflammation early in life, the current evidence is insufficient to justify the conclusion that FeNO testing in children ages 0 to 4 years reliably predicts a diagnosis of asthma at ages 5 years and older. Future studies may, however, demonstrate otherwise.

Although FeNO levels appear to reflect T2 inflammation early in life, T2 inflammation is not specific to asthma. FeNO levels in early childhood (ages 0–4 years) strongly correlate with API scores. This correlation is not surprising because of the relationship between atopy and FeNO levels and the fact that this index is heavily predicated on an atopic constitution. FeNO levels are higher in children with wheezing than in children without a recent history of wheezing and in children with persistent wheezing than in those with transient wheezing. Because most children with transient wheezing stop wheezing by age 3 years,[88,89] young children who continue to wheeze after age 3 years are more likely to develop asthma in the future. Four studies ascertained whether elevated FeNO levels in children younger than 5 years predicted a future diagnosis of asthma. The studies, which used FeNO and other clinical measures in different models, had mixed results (see EtD Table III). One longitudinal study[87] is ongoing and may provide new information on this issue.

Rationale and Discussion

FeNO can be measured in young children who have normal resting breathing, and normal reference values for FeNO have been published for children ages 1–5 years.[90] Evidence shows that in some preschool children with recurrent coughing and wheezing, an elevated FeNO level more than 4 weeks after an upper respiratory tract infection may help predict physician-diagnosed asthma at school age, independently of clinical history or presence of immunoglobulin E.[78-87] However, the studies reviewed for this update had conflicting results, and in the opinion of the Expert Panel, they provided low to moderate certainty for an asthma diagnosis.

A single FeNO measurement to predict future asthma is not likely to be physically harmful and is not burdensome. However, unreliable prediction models risk jeopardizing future insurability and could lead to treatment decisions that might rely on inadequate measures. Until better data on the predictive ability of FeNO measurement are available for children ages 0–4 years, clinicians should inform parents that the data are limited to support the use of FeNO measurement for this purpose.

The Expert Panel appreciates the potential value of a noninvasive tool to predict asthma onset, but such testing may cause worry and adversely affect care and treatment if the findings are inaccurate. In the Expert Panel's judgment, therefore, the acceptability of FeNO measurement for predictive purposes is low. Use of this testing is unlikely to change current treatment standards and could actually misdirect care. The feasibility of implementing FeNO measurement in this population seems challenging for several reasons, including the likely need for a specialist, not a primary care provider, to do the measuring because of the difficulty of ensuring proper technique and accurate results. In addition, the cost and maintenance requirements of FeNO equipment may limit the test's use.

Given that the Expert Panel recommends against the use of FeNO measurement to predict future asthma diagnoses in this population, equity issues are not expected to arise. However, if the test is marketed to patients who have private insurance or who pay for health care out of pocket, it could adversely impact those individuals. Therefore, the Expert Panel believes that the balance of effects does not favor the use of FeNO for predicting future asthma diagnoses in young children.

Future Research Opportunities

The value and potential are clearly high for new methods to evaluate individuals with wheezing, correctly identify those with asthma, select appropriate asthma therapy, and monitor responses to asthma therapy. Research on FeNO measurement and its use in asthma has advanced since the *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* was published. To expand this research, further clarify the role of FeNO measurement for asthma diagnosis in individuals with wheezing, and use FeNO measurement to support the care of individuals with asthma, topics for future research include the following:

- Use of FeNO measurement in the diagnostic process (e.g., to determine the point at which FeNO testing should be used in relation to other diagnostic tools and which individuals with asthma ages 5 years and older should be tested)
- Prevalence of asthma in the settings in which the Expert Panel recommends FeNO measurement (e.g., specialty care settings) to better understand the performance of FeNO testing as a diagnostic tool
- Use of FeNO testing to monitor adherence of children and adults to ICS and other anti-inflammatory treatments
- Role of FeNO measurements in children ages 0–5 years who have wheezing or asthma-like symptoms to predict subsequent asthma diagnoses
- Role of point-of-care FeNO measurement to identify children who do not require oral corticosteroid therapy
- FeNO-based asthma management in people with moderate to severe persistent asthma
- Potential uses of FeNO measurement for asthma management in primary care
- Impact on asthma health disparities of differential access to FeNO measurement because of lack of health care coverage
- Cost-effectiveness of FeNO measurement in diverse populations and clinical settings
- Role of FeNO testing in individuals with uncontrolled asthma to predict the benefit of adding T2-directed biologic therapies
- Refinement and validation of FeNO cutoff levels for diagnostic purposes (e.g., by determining variations in FeNO levels in individuals with different comorbid conditions, physiological determinants of FeNO levels, and FeNO levels in different ethnic and racial groups)
- Identification of algorithms for the most useful combination of, and cutoff levels for, objective measures (e.g., FeNO levels, blood eosinophil levels, spirometry test results, short-acting $beta_2$-agonist use, symptom scores) for choosing, monitoring, or adjusting anti-inflammatory therapy
- Refinement of ongoing management strategies that incorporate FeNO measurement to better understand the optimal timing and interpretation of FeNO levels in a range of asthma phenotypes (e.g., eosinophilic vs. noneosinophilic asthma)
- Identification of the populations most likely to benefit from FeNO-guided treatment and the optimal frequency of FeNO monitoring

SECTION III

Recommendations for Indoor Allergen Mitigation in Management of Asthma

Background

Environmental control is one of the four cornerstones of asthma management in *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.*[12] The Expert Panel was tasked with examining the effectiveness of single-component and multicomponent allergen mitigation strategies directed at common, indoor aeroallergens, with the goal of improving asthma outcomes for individuals with asthma. The key questions for this priority topic and the recommendations by the Expert Panel are provided for single-component and multicomponent allergen mitigation strategies.

Not included in the scope of work for this priority topic is an examination of the utility of clinical testing for sensitivity to allergens (e.g., using skin prick tests or tests of allergen-specific immunoglobulin E [IgE]), mitigation strategies for outdoor allergens, and mitigation of environmental irritants (e.g., tobacco smoke). Specific occupational exposures were also outside the scope of work, although the indoor allergens addressed in these recommendations can be encountered in work settings.

Definitions of Terms Used in this Section

An allergen mitigation intervention aims to decrease an individual's exposure to allergens. The intervention can have a single component or multiple components.

A single-component intervention is an individual mitigation strategy targeted at one or more specific allergens to which an individual is both exposed and sensitized. Single-component allergen mitigation interventions examined in this report include the following:

- Acaricide: a house dust mite pesticide that can be applied to carpets, mattresses, and furniture Air-filtration systems and air purifiers, including those with high-efficiency particulate air-filtration (HEPA) filters: devices that filter indoor air and remove solid particulates, such as dust, pollen, mold, and bacteria, from the air
- Carpet removal: removal of wall-to-wall or area rugs from one or more rooms

- Cleaning products: including application of bleach or similar products
- HEPA vacuum cleaners: vacuum cleaners that have a HEPA filter
- Impermeable pillow and mattress covers: covers placed on mattresses and pillows that are impermeable to dust mites
- Integrated pest management: a comprehensive approach to removing and controlling common indoor pests (e.g., cockroaches and mice) using, for example, traps, poison, and barriers to influx. The Expert Panel considered integrated pest management to be a single-component intervention even though it may include prevention, mitigation, and removal strategies.
- Mold mitigation: professional removal, cleaning, sanitization, demolition, or other treatment to remove or prevent mold. The Expert Panel considered mold mitigation to be a single-component intervention even though it may include prevention, mitigation, and removal strategies.
- Pet removal: complete removal or confinement of furry pets (e.g., dogs and cats) to specific rooms in a house

A "multicomponent intervention" is defined as the use of two or more of the aforementioned single-component interventions at the same time as part of a bundled approach targeted at one or more allergens to which the individual is both sensitized and exposed. An example of a multicomponent intervention is the use of three single-component interventions (e.g., air purifiers, impermeable pillow and mattress covers, and HEPA vacuum cleaners) for individuals sensitized and exposed to dust mites and mold.

"Sensitization" is defined in this section as the production of a specific IgE to an aeroallergen whose presence can be confirmed by skin prick testing or assays for a specific IgE.

QUESTION 3.1

Among individuals with asthma, what is the effectiveness of interventions (e.g., pesticides, air filters/purifiers, mattress covers, pest control, etc.) to reduce or remove indoor inhalant allergens on asthma control, exacerbations, quality of life, and other relevant outcomes?

In some individuals, asthma can have an allergic component. Therefore, clinicians should take a history of the individual's environmental allergen exposure and pursue testing for specific allergen sensitization, when appropriate. The Expert Panel has several recommendations for this question:

Recommendation 5: In individuals with asthma who do not have sensitization to specific indoor allergens or who do not have symptoms related to exposure to specific indoor allergens, the Expert Panel conditionally recommends against allergen mitigation interventions as part of routine asthma management.

Conditional recommendation, low certainty of evidence

Recommendation 6: In individuals with asthma who have symptoms related to exposure to specific indoor allergens, confirmed by history taking or allergy testing, the Expert Panel conditionally recommends a multicomponent allergen-specific mitigation intervention.

Conditional recommendation, low certainty of evidence

Recommendation 7: In individuals with asthma who have sensitization or symptoms related to exposure to pests (cockroaches and rodents), the Expert Panel conditionally recommends the use of integrated pest management alone, or as part of a multicomponent allergen-specific mitigation intervention.

Conditional recommendation, low certainty of evidence

Recommendation 8: In individuals with asthma who have sensitization or symptoms related to exposure to dust mites, the Expert Panel conditionally recommends impermeable pillow/mattress covers only as part of a multicomponent allergen mitigation intervention, not as a single-component intervention.

Conditional recommendation, moderate certainty of evidence

Implementation Guidance

CLINICIAN'S SUMMARY:

For individuals with asthma who do not exhibit any allergy symptoms or for whom testing has not suggested that they have an allergy to certain indoor substances (e.g., dust mites or cat dander), the Expert Panel recommends no specific environmental interventions to reduce these allergens within the home.

For individuals with asthma who are exposed to an allergen within the home and who have allergy symptoms or a positive test result suggesting that they have an allergy to certain indoor substances (e.g., dust mites or cat dander), the Expert Panel recommends using a multicomponent intervention to try to control the indoor allergen in question. Single-component interventions often do not work.

For individuals with asthma who are exposed to cockroaches, mice, or rats in the home and who have allergy symptoms or sensitization to these allergens demonstrated by allergy skin testing or a specific IgE, the Expert Panel recommends using integrated pest management to improve asthma outcomes. Integrated pest management can be used alone or with other interventions to reduce exposure to pest-related allergens in the home.

For individuals with asthma who have allergy symptoms or a test result suggesting that they are allergic to dust mites, the Expert Panel recommends using multicomponent interventions to reduce dust mite levels in the home and improve asthma outcomes. Use of pillow and mattress covers alone does not improve asthma outcomes.

Overall, the studies of allergen mitigation strategies provide low certainty of evidence that these strategies are beneficial for key asthma outcomes. Therefore, the Expert Panel recommends tailored allergen intervention strategies only for individuals with asthma who are exposed to these specific allergens and have either symptoms based on clinical history or an allergy to these substances based on allergy testing.

Based on current data on the use of a variety of single-component and multicomponent strategies to reduce exposure to allergens, the Expert Panel makes the following suggestions for implementing allergen exposure reduction strategies:

- Allergen mitigation strategies can be used in individuals of all ages with asthma of all levels of severity.
- Clinicians need to tailor mitigation strategies to the individual based on their allergy symptoms, sensitization, and exposures. Clinicians should consider allergen testing when appropriate, before committing individuals to specific allergen mitigation strategies that may be burdensome. See Table III.a for allergen-specific mitigation interventions addressed in the systematic review report. Table III.b summarizes the certainty of evidence on various allergen mitigation interventions.
- The Expert Panel recognizes the existing inequities in access to specialists and allergen testing. The panel therefore advises clinicians to, at a minimum, take a clinical history of symptoms and exposures for all individuals with asthma to help determine the need for allergen mitigation.
- Allergy testing (with a skin prick or allergen-specific IgE test) may have false-positive and false-negative results, and certain allergens (e.g., dust) may also act as irritants. For an individual whose symptoms worsen on exposure to specific aeroallergens, the Expert Panel recommends that the clinician consider mitigating that aeroallergen even if the individual's test result is negative.
- Some of the interventions examined provide no or low certainty of evidence about their efficacy in improving asthma outcomes (including exacerbations, quality of life, asthma control, and symptoms). The Expert Panel recognizes that some of the interventions, especially integrated pest management and mold mitigation, may have broader public health benefits. However, these interventions do not replace routine good practices, including regular and frequent house cleaning and laundering of bedding materials.
- Some people are allergic to dander (flakes of skin) or saliva from pets. The few studies on pet removal have had inconclusive results. However, if an individual with asthma experiences symptoms around a pet, the individual should consider removing the pet from the home, keeping the pet outdoors, or, if neither of these options is feasible, keeping the pet out of commonly used rooms. Testing for sensitization to pets may be particularly worthwhile for those with chronic or uncontrolled symptoms and might help support what can be a difficult decision to remove a pet from the home.
- Some cleaning and integrated pest management interventions may trigger asthma and/or be hazardous. Individuals with asthma need to balance the potential benefits and harms of interventions before implementing them.
- If an individual with asthma has sensitization to an allergen on skin prick testing and is exposed to that allergen but has no objective evidence of worsened disease control and denies having symptoms, chronic exposure could have led to the development of clinical tolerance to that allergen in that environment. Allergen-specific mitigation strategies could adversely modify this established balanced relationship between the individual and the environment.

Table III.a: Examples of Allergen Mitigation Interventions and Their Targeted Allergens

Intervention assessed in studies in the SR	Animal dander	Dust mites	Cockroaches	Mold
Acaricide		++		
Air filtration systems and air purifiers	++	+	+	++
Carpet removal	++	++		+
Cleaning products (e.g., bleach)				++
HEPA vacuum cleaners	++	+	+	++
Impermeable pillow and mattress covers		++		
Integrated pest management	+*		++	
Mold mitigation				++
Pet removal	++			

++ Primary target allergen(s) for the intervention
+ Secondary target allergen(s) for the intervention
*Dander from rodents

Abbreviations: HEPA, high-efficiency particulate air (a type of filter); SR, systematic review.

Table III.b: Summary of Certainty of Evidence on Allergen Mitigation Interventions

Intervention assessed in studies in the SR	EtD table number	Evidence on use as a single-component strategy for allergen mitigation (certainty of evidence)	Evidence on use as part of a multicomponent strategy for allergen mitigation (certainty of evidence)*
Acaricide	IV	†	Intervention makes no difference (moderate certainty of evidence)
Impermeable pillow and mattress covers	V	Intervention makes no difference (moderate certainty of evidence)	Evidence favors intervention (moderate certainty of evidence)
Carpet removal	VI	†	Intervention makes no difference (low certainty of evidence)
Integrated pest management (for cockroaches and mice)	VII	Evidence favors intervention (low certainty of evidence)	Evidence favors intervention (low certainty of evidence)
Air filtration systems and air purifiers	VIII	Intervention makes no difference (low certainty of evidence)	Intervention makes no difference (moderate certainty of evidence)
HEPA vacuum cleaners	IX	†	Evidence favors intervention (among children only; moderate certainty of evidence)
Cleaning products	X	†	†
Mold mitigation	XI	†	Evidence favors intervention (low certainty of evidence)
Pet removal	XII	†	†

*Combination of interventions used in the multicomponent studies varied, and the Expert Panel cannot identify or recommend any particular combination of strategies as optimal at this time.

† Evidence was insufficient for the Expert Panel to assess the intervention.

Abbreviations: EtD, evidence to decision; HEPA, high-efficiency particulate air (a type of filter).

- **What clinicians should discuss with their patients and families:**

  - Clinicians need to consider the complexity of the patient population and the limitations of the evidence identified. Clinicians may also find it helpful to consider the severity of a patient's asthma, the small benefit, and the extent of previous symptoms and exacerbations when recommending allergen mitigation interventions.
  - Allergen mitigation interventions may be expensive or difficult for patients to use or maintain. Clinicians should consider the cost implications of certain interventions, especially among those with limited financial resources, and assess the magnitude of the potential value of an intervention in improving an individual's asthma outcomes.

Summary of the Evidence

The Expert Panel specified four outcomes (exacerbations, asthma quality of life, asthma control, and asthma symptoms) as *critical* outcomes when it reviewed the evidence. The panel considered outcomes related to health care utilization to be important outcomes. The Expert Panel gave higher priority to outcomes measured in studies that used validated outcome instruments than those assessed with nonvalidated outcome measures. When data on validated outcome measures were not available, the Expert Panel used data from nonvalidated outcome measures, such as asthma symptoms. Table III.b summarizes the Expert Panel's assessments of the certainty of evidence for each of the allergen mitigation interventions examined, when used as a single-component intervention or as part of a multicomponent intervention. The table also lists the EtD tables for each of the interventions.

Single-Component Allergen Mitigation Interventions

For the majority of single-component allergen mitigation interventions, studies to assess the effectiveness of the interventions were limited. For the single-component interventions with enough studies to assess their impact on critical outcomes, the certainty of the evidence was either low or very low, or the results were limited to one or two critical outcomes on which results were inconclusive or that did not improve. The studies included mixed populations, which made it difficult to determine whether better-defined populations might benefit from the intervention. Certainty of evidence was often downgraded because of the limitations of several studies, including those of single-component interventions with acaricides[91,92] and air purifiers.[93-96] These limitations included insufficient descriptions of the randomization scheme, absence of a placebo intervention, and imprecision related to small sample size. No single-component intervention studies examining HEPA vacuum cleaners, carpet removal, or mold mitigation were available for review. The evidence was insufficient to allow the Expert Panel to examine the use of cleaning products.[97] In contrast, dust mite mitigation using impermeable mattress and pillow covers as a single intervention was the subject of many RCTs, which yielded moderate certainty of evidence of no benefit for the critical outcomes, including asthma symptoms.[98-109] Results for pet removal were inconclusive.[110]

Based on these studies, the Expert Panel made a conditional recommendation against most single-component allergen mitigation interventions as part of routine asthma management for individuals without specific identified triggers or exposure. The Expert Panel also included in the recommendation a conditional recommendation against impermeable pillow and mattress covers as a single-component allergen mitigation intervention.

One RCT and one pre- and postintervention study suggested that integrated pest management for cockroaches and rodents reduces the number of asthma exacerbations but has no effect on asthma control.[111,112] As a result, the Expert Panel made a conditional recommendation in favor of using integrated pest management as a single-component allergen mitigation strategy based on the evidence showing a reduction in asthma symptoms (low certainty of evidence). The Expert Panel also noted the importance of pest control as an established public health principle and practice.

Multicomponent Allergen Mitigation Interventions

The effectiveness of multicomponent mitigation interventions was difficult to evaluate because of inconsistencies in the designs used in different studies. Studies on most multicomponent interventions demonstrated minimal or no improvement in *critical* outcomes. Some studies did, however, demonstrate a reduction in asthma symptoms. The systematic review, using a qualitative comparative analysis, was unable to determine whether specific combinations of interventions were necessary or sufficient to improve the outcomes of interest.[4]

For multicomponent interventions that included integrated pest management, results were mixed. These studies provided high certainty of evidence of no reduction in exacerbations, although the same studies provided moderate to low certainty of evidence of a reduction in asthma symptoms and exacerbations when a composite measure was used. When examined in the context of a multicomponent intervention, acaricides had no effect on asthma symptoms (high certainty of evidence) and had inconclusive results for exacerbations (very low certainty of evidence).[113-117] Multicomponent intervention studies that included the use of HEPA vacuum cleaners had mixed results; some RCTs demonstrated a change in exacerbations, asthma-related quality of life, or asthma symptoms.[118-123] Most of the studies that demonstrated improvements in critical outcomes using HEPA vacuum cleaners were conducted in children.

In multicomponent studies that included air filtration systems and air purifiers (three of the four studies used devices with HEPA filters), the results showed no decrease in exacerbations or improvement in quality of life (high certainty of evidence). The results were mixed for asthma control (no benefit, low certainty of evidence) and asthma symptoms (decreased severity or number of reported symptoms in children but not in mixed populations, low certainty of evidence).[118,121,124,125]

Studies on the use of impermeable pillow and mattress covers as part of a multicomponent intervention strategy provided high certainty of evidence of a decrease in the number of asthma symptom days but did not show other benefits for any of the critical outcomes examined.[121,122,124-126] Studies using a composite score for asthma symptoms or cough and wheeze frequency provided very low to moderate certainty of no benefit of impermeable pillow and mattress covers, depending on the outcome examined.[113,114,116-118,121,122,127,128]

Some but not all study findings suggested that multicomponent interventions that included mold mitigation reduce symptoms to an extent.[129,130] The results of studies of multicomponent interventions that included pet removal were inconclusive.[115,130]

Most studies did not examine harms, and none reported any important harms from the various allergen mitigation strategies studied. Because of the lack of benefits identified and the potential harms from applications of chemicals, the Expert Panel does not recommend use of acaricides.

Rationale and Discussion

Overall Approach for Developing Allergen Mitigation Recommendations

When developing each of the four recommendations in this section, the Expert Panel considered the benefits and harms of each of the allergen mitigation interventions and the level of evidence available for assessing the interventions. In addition, the Expert Panel considered the acceptability of the interventions to individuals with asthma and their providers as well as the ease of use, costs, and impact on health equity of each intervention.

Potential Harms

Although the identified harms from most of the interventions were minimal, studies rarely examined harms. Therefore, the Expert Panel considered theoretical harms, patient burden, and initial and ongoing costs in its recommendations. For example, the Expert Panel's judgment was that interventions for mold mitigation and carpet removal could be associated with risks or be costly or difficult to complete. Another Expert Panel determination was that impermeable pillow and mattress covers are low-risk interventions with limited costs but are likely to require frequent cleaning of the bedding above the covers to be effective.

Prioritization of Outcomes

Furthermore, the Expert Panel considered the impact of the interventions on asthma symptoms as a *critical* outcome. The Expert Panel recognized that none of the studies used a validated outcome measure of asthma symptoms, and the definition of asthma symptoms was not standardized across studies. However, asthma symptoms are a relevant patient-centered outcome that was important to individuals with asthma in focus groups and that could be particularly relevant to assess for low-risk interventions.

Heterogeneity of Studies

The Expert Panel found the heterogeneity of available studies to be challenging. As outlined in the allergen reduction systematic review report,[4] participants' baseline clinical characteristics were variable, and the findings from these studies suggested that participants were not equally likely to benefit from the interventions reviewed.

In addition, the Expert Panel preserved the systematic review report authors' distinction between single-component interventions designed to mitigate a single allergen (e.g., an acaricide for house dust mite allergens); single-component interventions that address multiple allergens (e.g., air purifiers to control mold and animal dander); and multicomponent interventions, which usually target more than one allergen (see Table III.a).

Many of the studies available to the Expert Panel examined multicomponent interventions in mixed populations of patients with varying severities of asthma and sensitizations to allergens. Moreover, the combinations of components examined in each study were rarely the same across studies, and most studies did not assess adherence to or use of the interventions. The Expert Panel concurred with the systematic review report authors' assessment that the interplay between allergen type, intervention type, and individual patient characteristics could have strongly modified the effects of these interventions in these studies.

Targeting Recommendations to Individuals Who Are Both Exposed and Allergic to Specific Allergens

It was the Expert Panel's judgment that individuals with asthma should not burden themselves with allergen mitigation interventions if they are both not regularly exposed to an allergen and not allergic to a specific allergen. Given that certain populations might not have ready access to allergy specialists and allergen skin prick or IgE testing, the Expert Panel noted that patient histories (e.g., symptoms related to exposure to specific indoor allergens) to assess patient sensitivities could suffice. Therefore, the Expert Panel is not recommending allergen mitigation interventions for all individuals with asthma. Instead, the panel is recommending basing decisions about allergen mitigation interventions on a combination of the exposures, symptoms, and sensitization of individuals with asthma.

Single-Component Interventions are Rarely Effective

Of the single-component allergen mitigation interventions evaluated in enough studies to assess their impact on *critical* outcomes, the certainty of the evidence was either low or very low, or the results were limited to one or two critical outcomes, were inconclusive, or demonstrated no improvement. As summarized in Table III.b, the Expert Panel considered integrated pest management to be a single-component intervention, and it was the only single-component approach with beneficial effects. Single-component dust mite interventions using pillow and mattress covers demonstrated no benefit for any of the *critical* outcomes, including asthma symptoms. Based on these findings, it was the Expert Panel's judgment that single-component approaches to mitigating an allergen are rarely effective.

Evidence for Multicomponent Interventions Varies

Across the allergen mitigation interventions examined in this report, it was the Expert Panel's judgment that mattress and pillow covers, integrated pest management, HEPA vacuum cleaners, and mold mitigation are potentially beneficial when used as part of a multicomponent allergen mitigation strategy, but the benefits are small. Mattress and pillow covers as part of a multicomponent allergen mitigation strategy did not show improvements when validated outcome measures (e.g., exacerbations, Asthma Control Test, or Asthma Quality of Life Questionnaire) were used. The strength of evidence from the studies demonstrating small reductions in symptom days (a nonvalidated outcome measure) and the low risk and relative cost of impermeable pillow and mattress covers resulted in the Expert Panel's conditional recommendation for use of this intervention only as part of a multicomponent allergen mitigation strategy.

The evidence was stronger on improvements across asthma outcomes for both integrated pest management and HEPA vacuum cleaners used as part of a multicomponent strategy than the evidence on impermeable mattress and pillow covers.

Only three studies examined multicomponent interventions that included mold mitigation.[129-131] The Expert Panel considered the reduction in health care utilization with mold mitigation as well as the broader public health benefit of supporting its use as part of a multicomponent allergen mitigation strategy in making its conditional recommendation.

Additional Considerations

For most of these interventions, the certainty of evidence is low, and the benefits are small. It is not the Expert Panel's intent to suggest that all four of these interventions (mattress and pillow covers, integrated pest management, HEPA vacuum cleaners, and mold mitigation), when used as part of a multicomponent strategy, serve as the optimal allergen mitigation package. Instead, the Expert Panel is indicating that individuals who have symptoms related to exposure to specific allergens should consider using these interventions when appropriate.[129]

The Expert Panel recognizes that patients, providers, and other stakeholders generally find mattress and pillow covers to be an acceptable, noninvasive strategy to reduce exposure to dust mites. However, the Expert Panel cautions individuals with asthma not to use these covers as the sole strategy for mitigating dust mites. Studies that applied mattress and pillow covers solely either showed no effect on asthma outcomes or had inconclusive results. It was the Expert Panel's judgment that mattress and pillow covers should only be applied as part of a multicomponent intervention targeting dust mites.

In summary, the studies of allergen mitigation strategies provided lower certainty of evidence of effectiveness for key asthma outcomes than studies of asthma controller medications. For these reasons, the Expert Panel recommends only tailored allergen intervention strategies for individuals with asthma who have symptoms related to exposure confirmed by allergy testing or clinical history for identified indoor allergens.

Future Research Opportunities

The Expert Panel has identified the following topics related to allergen mitigation interventions (e.g., acaricides, air purifiers, HEPA vacuum cleaners, carpet removal, pet removal, cleaning products, and mold mitigation) that require additional research:

- Effectiveness of allergen mitigation interventions that use the validated outcome measures recommended by the Asthma Outcomes Workshop[10]

- Effectiveness of allergen mitigation interventions in individuals with asthma who have demonstrated exposure and/or sensitization to these allergens at home, school, or work
- Multicomponent interventions targeted to specific allergens in study populations consisting only of people with demonstrated sensitization and exposure to those allergens
- Comparisons of different combinations of multicomponent interventions to determine the optimal combination(s) of allergen-specific mitigation strategies that improve outcomes
- Studies to determine the allergen reduction thresholds for symptoms
- Interactions and necessity of exposure, sensitization, and symptoms to determine which individuals with asthma will benefit most from allergen mitigation strategies (e.g., whether an allergen-specific mitigation strategy is beneficial for an individual with asthma who has sensitization on skin prick testing to an allergen, is exposed to that allergen, and denies having symptoms)

In addition, reports of studies on the effectiveness of allergen mitigation interventions must include details on the intervention studied (e.g., the models of air purifiers used) and the protocols for using the intervention (e.g., how often the air purifier was turned on, where it was located, and how often the filter was changed). These aspects of the intervention need to be measured, and levels of adherence to the protocol need to be reported.

SECTION IV

Recommendations for the Use of Intermittent Inhaled Corticosteroids in the Treatment of Asthma

Background

Scheduled, daily inhaled corticosteroid (ICS) treatment is the currently preferred pharmacologic controller therapy for persistent asthma in individuals of all ages.[12] *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3), published in 2007, suggested that intermittent ICS dosing schedules may be useful in some settings, but the evidence at that time was insufficient to support a recommendation in favor of this treatment beyond a recommendation based on expert consensus.[12]

Definitions of Terms Used in this Section

"Intermittent" ICS dosing in this section includes courses of ICS treatment used for brief periods, usually in response to symptoms or as an add-on with or without a long-acting beta$_2$-agonist (LABA). "Intermittent ICS dosing" does not refer to a single regimen, and its definition is specified in each of the recommendations. Intermittent ICS dosing allows providers to prescribe specific doses, frequencies, and durations of ICS use. When to use intermittent ICS dosing could depend on an individual's decision (based on need, which is also known as "as-needed" or "PRN" dosing), a predefined index showing worsening asthma, or some other predefined criterion.

"Controller therapy" refers to medications that are taken daily on a long-term basis to achieve and maintain control of persistent asthma.[12] Both controller therapy and intermittent dosing may involve daily use of a specific dose of an ICS. The terms "ICS-LABA" and "ICS-formoterol" indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler.

"Quick-relief" therapy refers to medications (e.g., an inhaled short-acting beta$_2$-agonist [SABA]) used to treat acute symptoms or exacerbations.[132] In this section, "as-needed" dosing (e.g., of a SABA) is intermittent and is based on the patient's decision (Figures I.b, I.c, and I.d).

The definitions of "low-," "medium-," and "high-dose" ICS are based on the recommendations from EPR-3.[12]

The term "puff" refers to a single actuation and inhalation of a medication delivered through any type of inhaler.

"Recurrent wheezing" as used for the studies included in this section is defined as three or more episodes of wheezing triggered by apparent respiratory tract infections in a child's lifetime or two episodes in the past year.

Overview of Key Questions and Recommendations for Intermittent ICS Use

Given the range of options for intermittent ICS dosing and the number of comparisons embedded in the three key questions for this priority topic, the Expert Panel made five recommendations for intermittent ICS use to address these key questions. The majority of the studies in the systematic review report[6] on this topic used comparative efficacy designs as opposed to comparative effectiveness designs.

Table IV provides an overview of the questions on this topic, interventions and comparators that the Expert Panel considered, and resulting recommendations. As shown, in the opinion of the Expert Panel, the evidence was insufficient to support recommendations for all of the comparators in the questions.

Table IV – ICS Key Questions and Recommendations

Question	Intervention	Comparator	Recommendation	Certainty of Evidence
4.1	Short-course daily ICS + as-needed SABA at start of RTI (Step 1)	As-needed SABA alone	Recommendation 9: Conditional, in favor of the intervention for ages 0–4 years	High
		Daily ICS	No recommendation*	
		No therapy	No recommendation*	
4.2	As-needed, concomitantly administered ICS + SABA	Daily ICS + as-needed SABA (Step 2)	Recommendation 10: Conditional, in favor of either the intervention or the comparator for ages 12 years and older	Moderate
			No recommendation* for ages 4–11 years	
	Intermittent, higher-dose ICS		Recommendation 11: Conditional, against the intervention for ages 4 years and older	Low

*Insufficient evidence

Question	Intervention	Comparator	Recommendation	Certainty of Evidence
4.3	Daily and as-needed ICS-formoterol (Steps 3 and 4)	Daily same-dose ICS + as-needed SABA	No recommendation* for ages 4 years and older	
		Daily higher-dose ICS + as-needed SABA	Recommendation 12: Strong, in favor of the intervention for ages 4 years and older	Moderate for ages 4–11 years
				High for ages 12 years and older
		Daily same-dose ICS-LABA + as-needed SABA	Recommendation 12: Strong, in favor of the intervention for ages 4 years and older	Moderate for ages 4–11 years
				High for ages 12 years and older
		Daily higher-dose ICS-LABA + as-needed SABA	No recommendation* for ages 4–11 years	
			Recommendation 13: Conditional, in favor of the intervention for ages 12 years and older	High for ages 12 years and older

*Insufficient evidence

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, short-acting beta$_2$-agonist; RTI, respiratory tract infection

In the remainder of this section, each key question is followed by recommendations that are relevant to the question, the evidence that supports the recommendation, and guidance for implementing each recommendation. The Expert Panel did not address the efficacy and safety of the following types of intermittent ICS treatment because they were not mentioned in the key questions:

- As-needed ICS-formoterol versus as-needed SABA in Step 1 (intermittent asthma) or Steps 5 and 6 (severe asthma) treatment (Figures I.b, I.c, and I.d)
- As-needed ICS-formoterol versus low-dose ICS treatment and as-needed SABA in Step 2 (mild persistent asthma) treatment (Figures I.b, I.c, and I.d)

Question 4.1

What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic, or nonpharmacologic therapy in children ages 0 to 4 years with recurrent wheezing?

Recommendation 9: In children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections, the Expert Panel conditionally recommends starting a short course of daily ICS at the onset of a respiratory tract infection with as-needed SABA for quick-relief therapy compared to as-needed SABA for quick-relief therapy only.

Conditional recommendation, high certainty of evidence

Implementation Guidance

CLINICIAN'S SUMMARY:

This recommendation is for children ages 0–4 years who have had three or more episodes of wheezing triggered by apparent respiratory tract infections in their lifetime or who have had two such episodes in the past year and are asymptomatic between respiratory tract infections. For this population, the Expert Panel recommends a short (7–10 day) course of ICS daily along with as-needed SABA for quick-relief therapy starting at the onset of signs and symptoms indicating a respiratory tract infection. Respiratory tract infections were not confirmed by culture or polymerase chain reaction in the studies, and no further details on wheezing were provided.

The Expert Panel makes the following suggestions for implementation of intermittent ICS dosing in children ages 0–4 years:

- One regimen used in two studies[133,134] is budesonide inhalation suspension, 1 mg, twice daily for 7 days at the first sign of respiratory tract infection-associated symptoms.
- Although the efficacy of intermittent ICS dosing has high certainty of evidence, data regarding effects on growth are conflicting. Clinicians should carefully monitor length or height in children treated with the recommended regimen.
- Caregivers can initiate intermittent ICS treatment at home without a visit to a health care provider when they have clear instructions. Clinicians should give caregivers written instructions on how to implement the recommended action plan at the onset of a respiratory infection. In addition, clinicians should review the plan with the caregiver at regular intervals.
- Clinicians should consider this intervention in children who are not taking daily asthma treatment at the first sign of respiratory tract infection-associated symptoms.

- **What clinicians should discuss with caregivers:**
  - Caregivers should be confident in the use of the asthma action plan because they will need to decide when to start treatment (i.e., at the onset of a respiratory tract infection).
  - The main potential benefit of intermittent ICS use during respiratory tract infections is the reduction in exacerbations requiring systemic corticosteroids. Clinicians should inform caregivers that this treatment could affect growth, and they should carefully monitor growth in children who use this recommended treatment. Clinicians should reconsider implementing this recommended treatment if any evidence shows a reduced growth rate that cannot be attributed to other factors (e.g., oral corticosteroid treatment). As part of shared decision-making, some parents may weigh the potential benefits and harms differently and may not choose this therapy because of concerns related to their child's growth.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and one *important* outcome (rescue medication use) for this question. The summary of evidence for Recommendation 9 is in evidence to decision (EtD) Table XIII in Appendix B.

Three randomized controlled trials (RCTs) with high certainty of evidence[133,135,136] compared SABA alone to intermittent ICS with SABA for quick relief. This treatment resulted in a 33 percent relative risk (RR) reduction in exacerbations requiring systemic corticosteroids. Two of these three trials assessed growth but found different effects on this outcome. Ducharme et al. found a 5 percent lower gain in height and weight in study participants receiving intermittent fluticasone (750 mcg twice daily at onset of a respiratory tract infection for up to 10 days) than in participants receiving a placebo.[135] The authors noted a significant correlation between the cumulative dose of fluticasone and changes in height. In contrast, Bacharier et al. did not find an effect on linear growth of budesonide inhalation suspension (1 mg twice daily for 7 days) in comparison with placebo in children with an "identified respiratory tract illness."[133] Whether these differences in growth effects were due to differences in drugs, doses, duration of treatment, or other factors is not clear.

Rationale and Discussion

The main comparator for which data are available is SABA-only therapy. The demonstrated efficacy but conflicting data regarding the effect of a short course of a daily ICS with SABA for quick-relief therapy on growth led the Expert Panel to develop a conditional recommendation for this therapy starting at the onset of an apparent respiratory tract infection for children ages 0–4 years with recurrent wheezing. Although one study that compared short ICS courses with regular daily ICS treatment showed no differences in exacerbations requiring systemic corticosteroids with moderate certainty of evidence, the Expert Panel made no recommendation based on this comparison because this study was not adequately powered to demonstrate equivalence.[134] No studies produced robust data on comparisons of intermittent ICS use with no treatment or a nonpharmacologic therapy.

Question 4.2

What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in individuals ages 5 years and older with persistent asthma?

Recommendation 10: In individuals ages 12 years and older with mild persistent asthma, the Expert Panel conditionally recommends either daily low-dose ICS and as-needed SABA for quick-relief therapy or as-needed ICS and SABA used concomitantly.

Conditional recommendation, moderate certainty of evidence

Implementation Guidance

CLINICIAN'S SUMMARY:

For individuals ages 12 years and older with mild persistent asthma, the Expert Panel recommends either of the following two treatments as part of Step 2 therapy: a daily low-dose ICS and as-needed SABA for quick-relief therapy or intermittent as-needed SABA and an ICS used concomitantly (i.e., one after the other) for worsening asthma. In this recommendation, "intermittent" ICS dosing is defined as the temporary use of an ICS in response to worsening asthma in an individual with asthma who is not taking ICS controller therapy regularly. This recommendation does not apply to ages 5–11 years because this therapy has not been adequately studied in this age group.

The Expert Panel makes the following suggestions for implementation of intermittent ICS dosing in individuals ages 12 years and older:

- Individuals ages 12 years and older with mild persistent asthma who are not taking asthma treatment may benefit from this therapy. The Expert Panel has made no recommendation for children ages 0–4 years or 5–11 years with mild persistent asthma because of insufficient evidence.
- Individuals ages 12 years and older with asthma and a low or high perception of symptoms may not be good candidates for as-needed ICS therapy. Regular low-dose ICS with SABA for quick-relief therapy may be preferred for such patients to avoid ICS undertreatment (low symptom perception) or overtreatment (high symptom perception).
- Based on the regimen assessed in three of the four studies on intermittent ICS dosing,[40,137,138] one approach to intermittent therapy is two to four puffs of albuterol followed by 80–250 mcg of beclomethasone equivalent every 4 hours as needed for asthma symptoms. In these studies, the clinician determined the dosing a priori. Currently, these medications need to be administered sequentially in two separate inhalers, but combination inhalers with albuterol and an ICS may be available in the United States in the future.
- Individuals who use this type of therapy can initiate intermittent therapy at home. However, they should receive regular follow-up to ensure that the intermittent regimen is still appropriate.
- **What clinicians should discuss with patients and families:**
  - Clinicians should inform individuals that the two treatment options do not have different effects on asthma control, asthma quality of life, or the frequency of asthma exacerbations when studied in large groups of people. Similarly, side effects are equally infrequent with daily and intermittent use.
  - Shared decision-making will allow the best choice to be made for a particular individual.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and one *important* outcome (rescue medication use) for this question. The summary of evidence for Recommendation 10 can be found in EtD Table XIV in Appendix B.

The studies showed no differences in asthma control, quality of life, or use of rescue therapy with the two types of intermittent ICS therapy (ICS paired with albuterol in two studies and ICS for worsening asthma symptoms in one study) and daily ICS treatment in three studies with high certainty of evidence in individuals ages 12 years and older.[40,138,139] The three studies also showed no differences in numbers of exacerbations between groups, but the strength of evidence on exacerbations was low. However, none of these studies was powered as an equivalence study, so the Expert Panel issued a conditional recommendation.

The Expert Panel made no recommendation for children ages 4–11 years because only low certainty of evidence was available from one small study by Martinez et al. that addressed this question in this age group (EtD Table XV).[140] Although the systematic review report[6] included one study in children ages 5–10 years, this study was not included in the EtD tables. In that study, all children received regular ICS treatment for 6 months. For the next 12 months, children were randomized to receive either intermittent ICS treatment or continued daily low-dose ICS treatment. Children in the continuous ICS group experienced significantly fewer exacerbations per individual (0.97) than those in the intermittent group (1.69, $P = 0.008$). However, the intermittent group had a greater increase in height after 6 months than the group that maintained regular therapy during months 6–18.[141] The Expert Panel concluded that the use of regular ICS therapy for 6 months before intermittent therapy made this study's results difficult to interpret in the context of the key question.

Rationale and Discussion

Outcomes did not differ in the groups treated with the two alternate regimens in the three studies[40,138,139] in individuals ages 12 years and older. However, because none of these studies was powered as an equivalence study, the Expert Panel made a conditional recommendation. Although the studies had high certainty of evidence for asthma control and quality of life, they had low certainty of evidence for exacerbations and, taken together, resulted in overall low certainty for the recommendation statement. The Expert Panel made no recommendation based on this comparison for children ages 4–11 years because the only small included study in this population had low certainty of evidence, and one additional study had a study design that precluded evaluation for this key question.

Recommendation 11: In individuals ages 4 years and older with mild to moderate persistent asthma who are likely to be adherent to daily ICS treatment, the Expert Panel conditionally recommends against a short-term increase in the ICS dose for increased symptoms or decreased peak flow.

Conditional recommendation, low certainty of evidence

Implementation Guidance

Clinician's Summary:

This recommendation addresses temporary increases in the dose of an ICS that is otherwise taken as controller therapy in response to worsening asthma. For this recommendation, a short-term increase in ICS dose refers to a doubling, quadrupling, or quintupling of the regular daily dose. For individuals ages 4 years and older with mild to moderate persistent asthma who are likely to adhere to their daily ICS treatment, the Expert Panel does not recommend doubling, quadrupling, or quintupling the ICS dose for increased symptoms or decreased peak flow. Clinicians can consider quadrupling the regular daily dose for individuals ages 16 years and older whose adherence to daily therapy is not assured (see discussion section below).

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and one *important* outcome (rescue medication use) for this question. The summary of evidence for Recommendation 11 can be found in EtD Table XVI in Appendix B.

In children ages 4–11 years, increasing the ICS dose temporarily in response to worsening symptoms did not significantly reduce the rate of exacerbations or improve asthma quality of life in one study by Martinez et al.[140] The overall certainty of evidence ranged from low for exacerbations to moderate for quality of life. A more recent study in 254 children by Jackson et al.[142] also found no difference in the rate of exacerbations treated with systemic corticosteroids with a quintupling of the ICS dose at early signs of loss of asthma control. In this 48-week study, the growth rate in the intervention group was reduced, although this difference did not reach statistical significance ($P = 0.06$). The potential for growth suppression by the intervention and the absence of demonstrated efficacy of the intervention in the articles that the Expert Panel reviewed led to a recommendation against using this intervention in this age group. The Expert Panel rated the recommendation as conditional because of the limited number of studies available in this age group.

In individuals ages 12 years and older (EtD Table XVII), the intervention as implemented did not significantly reduce exacerbations or asthma hospitalizations. The certainty of evidence is low for both outcomes of exacerbations and asthma hospitalizations in the systematic review report. A large, more recent study by McKeever et al. showed a modest but significant reduction in time to severe exacerbation and in the rate of use of systemic corticosteroids in individuals with asthma whose action plan included a quadrupling of the ICS dose.[143] However, unlike the studies in the systematic review report, this study did not include a placebo group or use blinding, and the baseline adherence rate was low. Specifically, only 50 percent of participants in the quadruple-dose group and 42 percent in the non-quadruple-dose group had good adherence, according to the investigators. Because of the low adherence rate, it was not clear whether the increased ICS dose was effective or whether the initiation of ICS treatment in nonadherent participants influenced the results. Thus, based on the lack of efficacy in the studies in the systematic review report and the possible growth effects, the Expert Panel made a recommendation against a short-term increase in the ICS dose.

In the reviewed studies, the indication for increasing the ICS dose was decreased peak flow and/or increased symptoms. When increased, the ICS dose was doubled, quadrupled, or quintupled.[142-146]

Rationale and Discussion

In children ages 4–11 years, the intervention did not significantly reduce exacerbations or improve asthma quality of life in one study[140] in the systematic review report. The intervention's potential to suppress growth in a more recent study[142] and the lack of demonstrated efficacy of the intervention in either of the reviewed articles led to the Expert Panel's recommendation against this intervention in this age group.

In individuals ages 12 years and older, the intervention as implemented also did not significantly reduce exacerbations in three studies[144-146] in the evidence summary, but the certainty of evidence is low. The more recent study by McKeever et al. showed modest but significant reductions in time to severe exacerbation and rate of ICS use in individuals whose action plan included a quadrupling of the ICS dose.[143] However, unlike the studies in the AHRQ systematic review report, this study did not include a placebo group or use blinding, and the baseline adherence rate was low (42–50 percent). The adherence rate in the McKeever et al. study might be more similar to the adherence rates in routine clinical practice, whereas adherence rates in the RCTs[144-146] were probably higher than in most real-world settings. The verification code for this document is 369480

Thus, the Expert Panel believes that this recommendation applies most specifically to individuals who are likely to adhere to their daily ICS regimen. An increase in the ICS dose might be a reasonable strategy to include in the action plans of individuals whose adherence rates are less certain. How to assess adherence or the threshold for adequate adherence for this recommendation cannot be determined from the reviewed studies. Based on the study of McKeever et al. in individuals ages 12 years and older described in the previous paragraph,[143] the ICS dose could be quadrupled in the short term in individuals ages 16 years and older in response to an increased need for reliever therapy, greater interference of asthma with sleep, or a peak flow of less than 80 percent of the individual's normal level. The potential discrepancy between the efficacy and effectiveness studies described above and the overall low certainty of evidence led to a conditional recommendation for this age group as well.

Question 4.3

What is the comparative effectiveness of ICS with LABA used as both controller and quick-relief therapy compared to ICS with or without LABA used as controller therapy in individuals ages 5 years and older with persistent asthma?

Recommendation 12: In individuals ages 4 years and older with moderate to severe persistent asthma, the Expert Panel recommends ICS-formoterol in a single inhaler used as both daily controller and reliever therapy compared to either a higher-dose ICS as daily controller therapy and SABA for quick-relief therapy or the same-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy.

Strong recommendation, high certainty of evidence for ages 12 years and older, moderate certainty of evidence for ages 4–11 years