Implementation Guidance

Clinician's Summary:

In individuals ages 4 years and older, the preferred Step 3 (low-dose ICS) and Step 4 (medium-dose ICS) therapy is single-inhaler ICS-formoterol both daily and as needed. In the literature, inhaled ICS-formoterol is referred to as "single maintenance and reliever therapy (SMART)." This form of therapy has only been used with formoterol as the LABA. Formoterol has a rapid onset and a maximum total daily dose that allows it to be used more than twice daily.[147] The maximum total daily dose of formoterol should not exceed eight puffs (36 mcg) for ages 4–11 years and 12 puffs (54 mcg) for ages 12 years and older. SMART is administered with a single inhaler containing both formoterol and an ICS (primarily budesonide in the reviewed studies, but one study used beclomethasone). The regimens compared to address this key question required two inhalers: the controller (ICS or ICS-LABA) and the reliever (SABA). The recommended alternate therapy of maintenance ICS-LABA with SABA as quick-relief therapy does not need to be changed if it is providing adequate control. However, patients whose asthma is uncontrolled on such therapy should receive the preferred SMART if possible before moving to a higher step of therapy.

The Expert Panel makes the following suggestions for implementation of daily and intermittent combination ICS-formoterol in individuals ages 4 years and older:

- No patient characteristics exclude consideration of this option in individuals ages 4 years and older with asthma.
- The studies demonstrating reduced exacerbations (see below) enrolled individuals with a severe exacerbation in the prior year. The results suggest that such individuals are particularly good candidates for SMART to reduce exacerbations.
- SMART might not be necessary for individuals whose asthma is well controlled on alternate treatments, such as conventional maintenance ICS-LABA with SABA as quick-relief therapy.
- SMART is appropriate for Step 3 (low-dose ICS) and Step 4 (medium-dose ICS) treatment.
- ICS-formoterol should be administered as maintenance therapy with one to two puffs once to twice daily (depending on age, asthma severity, and ICS dose in the ICS-formoterol preparation) and one to two puffs as needed for asthma symptoms. The maximum number of puffs per day is 12 (54 mcg formoterol) for individuals ages 12 years and older and 8 (36 mcg formoterol) for children ages 4–11 years. Clinicians should advise individuals with asthma or their caregivers to contact their physician if they need to use more than these amounts.
- The calculation of the dose of formoterol was based on 4.5 mcg/inhalation, the most common preparation used in the RCTs reviewed.
- ICS-formoterol should not be used as quick-relief therapy in individuals taking ICS-salmeterol as maintenance therapy.

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

  - Clinicians should inform individuals with asthma and their caregivers that in studies, this intervention consistently reduced asthma exacerbations requiring unscheduled medical visits or systemic corticosteroids. In addition, this intervention improved asthma control and quality of life in some studies.
  - No differences have been documented in harms between this type of therapy and the comparators (ICS or ICS-LABA) in individuals ages 12 years and older. The reductions in exposure to oral corticosteroids and to ICS treatment in most studies suggest that the intervention might reduce future corticosteroid-associated harms.
  - In children ages 4-11 years, there may be a lower risk of growth suppression among those taking SMART versus daily higher-dose ICS treatment.
  - This recommendation might not be appropriate for some individuals with asthma for such reasons as cost, formulary considerations, or medication intolerance. However, the additional cost of the medication may be offset by the decrease in exacerbations and the associated improvement in quality of life and reduction in costs to both the patient and the payer.
  - A 1-month supply of ICS-formoterol medication that is sufficient for maintenance therapy may not last a month if the inhaler is used for reliever therapy as well. Providers, individuals with asthma, pharmacists, and payers need to be aware of this possibility and prescribe, plan, dispense, or provide coverage accordingly.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and one *important* outcome (asthma symptoms) for this question. The summary of evidence for Recommendation 12 can be found in evidence to decision (EtD) Tables XVIII and XIX in Appendix B.

SMART vs. Higher-Dose ICS Treatment in Ages 4 Years and Older (EtD Table XVIII)

Three large RCTs[148-150] (total N = 4,662) enrolled individuals ages 12 years and older who were being treated with a low- to medium- or medium-to-high-dose ICS. Study participants treated with SMART used daily budesonide-formoterol, 160/9 to 320/9 mcg, via a dry-powder inhaler. They took up to 10 rescue puffs of budesonide-formoterol (total daily dose of 12 puffs or 54 mcg formoterol). The investigators compared this intervention with daily budesonide, 320–640 mcg, along with SABA for quick-relief therapy. Rabe et al. showed a 51 percent RR reduction in exacerbations, whereas the rates were 35 and 43 percent RR reduction in Scicchitano et al. and O'Byrne et al., respectively. The latter two studies used a composite exacerbation score that included systemic corticosteroid use, hospitalizations, emergency department visits, increase in ICS or other medication doses, and peak expiratory flow less than 70 percent.[148-150] Collectively, these RCTs found an RR of 0.6 (range of 0.53 to 0.68) favoring SMART for asthma exacerbations (high certainty of evidence). The investigators of these studies did not report results from validated outcome measures of quality of life or asthma control. However, results for individual asthma control measures—including total asthma symptom scores, nighttime awakenings, symptom-free days, and asthma control days—significantly favored SMART. The overall doses of inhaled and oral corticosteroids were significantly lower with SMART (two- to fourfold less for inhaled ICS treatments).

Jenkins et al.[151] conducted a post-hoc analysis of these three studies in 1,239 participants ages 12 years and older with milder asthma (daily maintenance ICS dose equal to 400 mcg or less budesonide equivalent). The authors confirmed that SMART reduced exacerbations overall. However, in subgroup

analyses, participants with the mildest asthma at enrollment (based on rescue SABA use of less than one inhalation/day) showed a marginal and statistically nonsignificant benefit.

Another post-hoc analysis of one of the three RCTs (O'Byrne et al.[148]) included 224 children ages 4–11 years who used medium to high ICS doses (any brand, 200–500 mcg daily). The 118 participants in the SMART group were instructed to take budesonide-formoterol, 80/4.5 mcg once daily, as their baseline therapy, with up to seven additional rescue puffs (total daily dose of 36 mcg formoterol). The other 106 participants took budesonide, 320 mcg daily, with rescue SABA. In the SMART group, the RR for a composite exacerbation measure comprised of systemic corticosteroids, hospitalization, emergency department visits, and increase in ICS or other medication dose dropped by 57 percent (moderate certainty of evidence). The authors did not report on validated outcome measures of quality of life or asthma control, but nighttime awakenings declined significantly with SMART. SMART participants used a lower daily ICS dose (average 127 vs. 320 mcg/day in the fixed-dose budesonide group) and demonstrated significantly improved growth rates (adjusted mean difference of 1 cm compared with fixed-dose budesonide).[152]

SMART vs Same-Dose ICS-LABA Controller Therapy for Ages 4 Years and Older (EtD Table XIX)

For ages 12 years and older, the Expert Panel considered four blinded RCTs[148,153-155] and two unblinded RCTs[156,157] for this question. Collectively, these RCTs demonstrated a 32 percent reduction in exacerbations with SMART[148,153-157] (high certainty of evidence). Two of the studies employed validated asthma control measures (ACQ-5) and both demonstrated clinically significant improvements with SMART (high certainty of evidence).[155,157]

Three of the blinded studies enrolled a total of 7,555 participants with mild to severe persistent asthma. Participants were treated with 160/9 or 320/9 mcg budesonide-formoterol daily with up to 10 rescue puffs (total daily dose of 12 puffs or 54 mcg formoterol) of budesonide-formoterol (SMART) or rescue SABA.[148,153,155] In these three blinded studies, SMART significantly reduced exacerbations.

One of these three studies[153] demonstrated a statistically significant improvement in asthma control (based on ACQ-5). A second blinded study (N = 1,748) enrolled participants ages 18 years or older with poorly controlled asthma who took a moderate to high dose of an ICS or ICS-LABA. The SMART group took two puffs daily of beclomethasone-formoterol, 100/6 mcg, and up to six puffs of rescue beclomethasone-formoterol per day (total daily dose of 48 mcg formoterol). The comparison group used rescue SABA. The investigators actively managed both arms with dose titration. Although severe exacerbations and systemic corticosteroid use were significantly lower with SMART, asthma control scores (ACQ-7) did not differ significantly between groups.[154]

An unblinded study, Vogelmeier et al., enrolled 2,143 participants from Europe and Asia with poorly controlled asthma taking moderate to high ICS or ICS-LABA doses (500 mcg or more of budesonide, fluticasone, or equivalent).[157] They received either daily budesonide-formoterol, 640/18 mcg, with budesonide-formoterol rescue (SMART group) or daily fluticasone/salmeterol, 500/100 mcg, with SABA for quick-relief therapy. The investigators actively managed both arms with dose titration, and the study was unblinded. With SMART, the RR declined by 20 percent for exacerbations, defined as emergency department visits, oral corticosteroid days, and hospitalization. SMART also improved asthma control (measured by ACQ-5) and quality of life (measured by AQLQ), but these changes were not statistically significant. A reanalysis of these data in 404 participants in China, Korea, Taiwan, and Thailand had similar results; the RR reduction in exacerbation rates was 38 percent.[158]

Another blinded study, Patel et al., enrolled 303 participants in New Zealand who were at risk of severe exacerbations. Participants were treated with budesonide-formoterol, 800/24 mcg (by metered-dose inhaler), with one rescue puff of budesonide-formoterol (SMART) or SABA for quick-relief therapy. SMART reduced exacerbations and oral corticosteroid use but increased the use of ICS, and the associated improvement in asthma control (measured by ACQ-7) was not significant.[156]

For ages 4–11 years, one blinded RCT[152] used budesonide-formoterol, 80/4.5 mcg, with up to seven rescue puffs of budesonide-formoterol, 80/4.5 mcg (36 mcg total daily dose of formoterol; SMART) or SABA as quick-relief therapy. SMART reduced the RR for exacerbations by 72 percent (moderate certainty of evidence) and showed superiority in one unvalidated outcome measure of asthma control (nighttime awakenings). Growth rates and other safety measures did not differ between treatment groups.

Rationale and Discussion

Because the only SMART studied has included formoterol, the Expert Panel's recommendation favors the use of ICS-LABA combinations containing formoterol rather than those that contain ICS-salmeterol. Daily ICS-salmeterol remains an appropriate therapeutic option for individuals with moderate to severe persistent asthma, but the reviewed data suggest that the use of ICS-formoterol for maintenance and reliever therapy has superior efficacy, ease of use (because it is administered in a single inhaler rather than two separate inhalers), and perhaps safety as a result of reduced corticosteroid exposure. Other LABAs, including newer agents with a rapid onset, may be effective and safe to use for both maintenance and reliever therapy, but their efficacy and safety will need to be demonstrated in clinical studies. The number of studies available and the consistency of the evidence led the Expert Panel to make a strong recommendation to use ICS-formoterol in a single inhaler as both daily controller and reliever therapy.

Data were insufficient to compare ICS-formoterol as single maintenance and reliever therapy with same-dose ICS for daily controller therapy along with SABA for quick-relief therapy in individuals ages 4 years and older. However, multiple studies have demonstrated that adding any LABA to the same ICS dose is more effective than ICS therapy alone.[12] Thus, the lack of comparisons data on ICS-formoterol as single maintenance and reliever therapy vs. same-dose ICS and SABA for quick-relief therapy is of minimal clinical importance.

Recommendation 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 recommendation, high certainty of evidence

Implementation Guidance

Clinician's Summary:

In individuals ages 12 years and older, the preferred Step 4 therapy is single-inhaler ICS-formoterol used both daily and as needed. The maximum total daily dose of formoterol should not exceed 12 puffs (54 mcg) for ages 12 and older. The recommended alternate therapy of maintenance ICS-LABA along with SABA as quick-relief therapy does not need to be changed if it is providing adequate control. However, individuals whose asthma is uncontrolled on such therapy should receive the preferred SMART if possible before stepping up their treatment to a higher step of therapy.

In individuals ages 12 years and older with moderate to severe persistent asthma, combination ICS-formoterol used daily and intermittently is more beneficial than an increase in the daily ICS dose if they are already taking combination ICS-LABA (and as-needed SABA). The Expert Panel makes the following suggestions for implementation of daily and intermittent combination ICS-formoterol for individuals ages 12 years and older:

- This recommendation applies to all individuals with asthma ages 12 years and older.
- Individuals with asthma should use ICS-formoterol as maintenance therapy with one to two puffs once or twice daily (depending on asthma severity and ICS dose in the ICS-formoterol preparation). The additional rescue dose is one to two puffs as needed for asthma symptoms, up to a maximum of 12 puffs (54 mcg formoterol) per day. Clinicians should advise individuals with asthma to contact their physician if they need to use more than these amounts.
- The calculation of the dose of formoterol was based on 4.5 mcg/inhalation, the most common preparation used in the RCTs reviewed.
- Clinicians managing asthma should regularly assess individuals using this therapy.
- This therapy is appropriate for Step 4.
- Individuals with asthma should not use ICS-formoterol as reliever therapy if they are taking ICS-salmeterol as maintenance therapy.
- SMART might not be necessary for individuals whose asthma is well controlled with alternate treatments, such as conventional maintenance ICS-LABA with SABA as quick-relief therapy.
- For individuals ages 5–11 years, the evidence was insufficient to make a recommendation regarding SMART compared to higher-dose ICS-LABA. SMART with low- or medium-dose ICS therapy is preferred for children ages 5–11 years as opposed to same-, low-, or medium-dose ICS-LABA plus as-needed SABA as part of Step 3 and Step 4 therapy (Recommendation 12).
- **What clinicians should discuss with their patients:**
  - Clinicians should inform individuals with asthma and their caregivers that the major demonstrated benefits of combination ICS-formoterol used daily and as needed are reductions in asthma exacerbations requiring unscheduled medical visits and in use of systemic corticosteroids.
  - Clinicians should also inform individuals with asthma that studies found no difference in documented harms between this type of therapy and daily ICS-LABA.
  - Studies showed that combination ICS-formoterol reduces exposure to corticosteroids, suggesting that the intervention might reduce future corticosteroid-associated harms.
  - This recommendation might not be appropriate for some individuals for such reasons as cost, formulary considerations, or medication intolerance.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) for this question. The summary of evidence for Recommendation 13 can be found evidence to decision (EtD) Table XIX in Appendix B.

Two blinded RCTs (N = 5,481) compared SMART to higher-dose ICS-LABA[159,160] in individuals with asthma ages 12 years and older. SMART reduced the RR by 25 percent for exacerbations (high certainty of evidence). SMART also resulted in statistically significant reductions in corticosteroid use but had no significant effect on asthma quality of life or asthma control. As a result, the recommendation was conditional.[159,160]

Rationale and Discussion

Bousquet et al.[159] compared daily budesonide-formoterol (640/18 mcg) plus budesonide-formoterol reliever therapy (SMART) in participants ages 12 years and older with daily fluticasone-salmeterol (1000/100 mcg) plus SABA for quick-relief therapy, while Kuna et al.[160] compared daily budesonide-formoterol (320/9 mcg) plus budesonide-formoterol reliever therapy (SMART) with either daily budesonide-formoterol (640/18 mcg) or daily fluticasone-salmeterol (500/100 mcg) plus SABA for quick-relief therapy. These two studies showed significant reductions in exacerbations in the SMART groups in comparison with maintenance ICS-LABA along with SABA for quick relief-therapy. However, the studies found no differences between groups in asthma control or quality of life, and the lack of differences in these outcomes led to the Expert Panel's conditional recommendation. Data were insufficient to make a recommendation regarding whether SMART is superior to daily higher-dose ICS-LABA with SABA for quick-relief therapy in children ages 4–11 years.

The systematic review report for this topic also included five open-label, real-world clinical trials that compared daily budesonide-formoterol (160–320/4.5–9 mcg) plus budesonide-formoterol reliever therapy (SMART) with conventional best-practice treatment (total N = 5,056).[6,161-164] Active management levels varied in these studies. Because of the heterogeneity of the studies and lack of information regarding the type of therapy prescribed and used in the conventional best practice arms, the formal systematic review report did not include these studies. However, the Expert Panel decided to review these studies to compare the potential benefits of SMART with those of diverse approaches in real-world settings. In general, the real-world studies confirmed the results from the RCTs that used SMART.

Future Research Opportunities

The Expert Panel identified the following topics that would benefit from additional research:

- Differences by race and ethnicity in benefits and risks of the ICS recommendations
- Cost-effectiveness of the ICS recommendations
- Effects on growth of short ICS courses starting at the onset of an apparent respiratory tract infection in children ages 0–4 years who have recurrent wheezing triggered only by such infections
- Optimal short-course ICS regimen to use—on the basis of efficacy, effectiveness, and safety—at the onset of an apparent respiratory tract infection in children ages 0–4 years whose recurrent wheezing is triggered by respiratory tract infections
- Efficacy, effectiveness, and safety of a short ICS course starting at the onset of an apparent respiratory tract infection compared with daily ICS treatment in children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections

- Daily low-dose ICS treatment with SABA for quick relief versus as-needed ICS plus SABA administered concomitantly in children ages 4–11 years with mild persistent asthma
- Optimal dose of albuterol and ICS used for as-needed concomitant therapy in individuals with mild persistent asthma
- Effectiveness and safety of other rapid-onset LABAs in combination medications used for both daily controller and quick-relief therapy
- Combination ICS-formoterol as both daily controller and reliever therapy compared with higher-dose ICS-LABA as daily controller therapy and SABA for quick-relief therapy in children ages 4–11 years

Other recommended types of research included:

- Confirmation of the efficacy data supporting the ICS recommendations using additional real-world effectiveness studies in clearly defined populations using clearly defined treatment regimens
- Additional studies powered as equivalence studies to confirm the finding that daily low-dose ICS therapy with SABA for quick relief and concomitant as-needed ICS therapy plus SABA lead to similar outcomes in individuals with mild persistent asthma
- Real-world studies that monitor growth in children and adherence to evaluate the effectiveness and safety of quadrupling the ICS dose in individuals with mild to moderate persistent asthma taking daily ICS controller therapy who experience early signs of loss of asthma control

SECTION V

Recommendations for the Use of Long-Acting Muscarinic Antagonists for Asthma

Background

Long-acting muscarinic antagonists (LAMAs) comprise a pharmacologic class of long-acting bronchodilators. The role of LAMAs in the management of asthma was not addressed in *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*.[12] Since that report's publication in 2007, several trials have investigated LAMAs as controller therapy for individuals with asthma.

The Expert Panel examined the harms and benefits of LAMAs in individuals ages 12 years and older with uncontrolled persistent asthma and addressed three key questions.[165] The Expert Panel did not examine the role of LAMA treatment in children ages 6–11 years because the key questions and systematic reviews did not address this age group. With the exception of one study that examined the LAMA umeclidinium,[166] the randomized controlled trials (RCTs) reviewed by the Expert Panel used tiotropium bromide as the LAMA. At the time this report was written, tiotropium bromide (RESPIMAT®) was the only formulation of LAMA with U.S. Food and Drug Administration (FDA) approval for asthma treatment. The majority of LAMA studies used a comparative efficacy design, and not an effectiveness design, but the key questions were about effectiveness. Therefore, the clinical impact of LAMA treatment in real-world settings is not well understood. Table V provides an overview of the key questions and recommendations on LAMAs.

Table V: LAMA Key Questions and Recommendations

Question	Intervention	Comparator	Recommendation	Certainty of evidence
5.1	LAMA as an add-on to ICS controller therapy*	LABA as an add-on to same-dose ICS controller therapy	14: Conditional, against intervention	Moderate
		Montelukast as an add-on to same-dose ICS controller therapy*	No recommendation**	
5.2	LAMA as an add-on to ICS controller therapy*	Same-dose ICS controller therapy* + placebo	15: Conditional, in favor of the intervention	Moderate
		Increased ICS dose	No recommendation**	
5.3	LAMA as an add-on to ICS-LABA	Same-dose ICS-LABA as controller therapy*	16: Conditional, in favor of the intervention	Moderate
		Doubled ICS dose + LABA	No recommendation**	

*ICS controller therapy used daily
**Insufficient evidence

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist

Definitions of Terms Used in this Section

In this section, "controller therapy" refers to medications that are taken daily on a long-term basis to achieve and maintain control of persistent asthma.[12] The term "ICS-LABA" indicates therapy with both an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist (LABA), usually (and preferably) in a single inhaler.

Question 5.1

What is the comparative effectiveness of LAMA compared with other controller therapy as add-on therapy to inhaled corticosteroids (ICS) in individuals ages 12 years and older with uncontrolled persistent asthma?

Question 5.2

What is the comparative effectiveness of LAMA as add-on therapy to ICS controller therapy compared with placebo or increased ICS dose in individuals ages 12 years and older with uncontrolled persistent asthma?

Recommendation 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 recommendation, moderate certainty of evidence

Recommendation 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 recommendation, moderate certainty of evidence

Implementation Guidance

Clinician's Summary:

In individuals with asthma that is not controlled by ICS therapy alone, the Expert Panel recommends adding a LABA rather than a LAMA to an ICS. However, if the individual is not using or cannot use LABA therapy, adding a LAMA to an ICS is an acceptable alternative. Adding a LAMA to ICS controller therapy is more effective than using ICS controller therapy alone in individuals ages 12 years and older with uncontrolled persistent asthma. However, adding a LAMA to ICS controller therapy is not more efficacious than adding a LABA to ICS controller therapy, and adding a LAMA may increase the risk of harm, based on a single real-world study in Blacks.[167] Therefore the panel recommends preferentially adding LABA over LAMA to ICS. A LABA should not be used when the individual cannot tolerate it, the medication is contraindicated, the device that delivers the LABA is unsuitable for the individual, or the LABA is unavailable for insurance or supply reasons.

The Expert Panel makes the following suggestions on the use of LAMA therapy:

- A LAMA can be used as an add-on to ICS therapy in individuals ages 12 years and older with uncontrolled asthma therapy as part of Step 4 therapy, but add-on LABA therapy has a more favorable benefit–harm profile.
- Individuals at risk of urinary retention and those who have glaucoma should not receive LAMA therapy.
- The small increase in the potential risk of harms from a LAMA may outweigh its benefits in some individuals, particularly in Blacks.
- LAMA treatment requires appropriate use of specific inhaler devices. Clinicians should teach individuals with asthma how to use these devices appropriately.
- When clinicians prescribe LAMA therapy, they should prescribe this medication for long-term asthma control in the ambulatory setting. LAMA therapy does not have a role in the management of acute exacerbations of asthma in the ambulatory, emergency department, or inpatient settings.

- Clinicians should confirm the asthma diagnosis and address factors that often contribute to uncontrolled asthma before they consider intensifying therapy by adding a LAMA. For example, clinicians should identify and suggest ways to mitigate occupational and environmental triggers and ensure that individuals with asthma are using currently prescribed asthma controller therapy appropriately.
- **What clinicians should discuss with their patients about LAMA therapy:**
  - When discussing the addition of a LAMA versus a LABA for individuals already taking an ICS, clinicians should explain that the LABA is likely to be preferable.
  - Adding a LAMA to ICS controller therapy provides no more benefit than adding a LABA to ICS controller therapy, and may increase the risk of harm, based on a single real-world study in Blacks.
  - Clinicians should tell individuals with asthma that adding a LAMA to an ICS provides a small benefit compared to continuing the same ICS dose if the individual cannot use a LABA for any reason.
  - Individuals with asthma and glaucoma and those at risk of urinary retention should not use LAMA therapy.

Summary of the Evidence

The Expert Panel prespecified three *critical* outcomes (exacerbations, asthma control, and quality of life) and three *important* outcomes (rescue medication use, adverse events [harms], and mortality). The Expert Panel did not consider lung function (e.g., based on spirometry testing) to be a *critical* or *important* outcome for the LAMA studies that it reviewed.

The summary of evidence for Recommendation 14 can be found in evidence to decision (EtD) Table XX in Appendix B. The Expert Panel examined the efficacy of adding a LAMA to ICS therapy in comparison with adding a LABA to ICS therapy in seven RCTs.[166-172] Five RCTs[166,168-170] that had a total of 2,574 participants found no difference in the exacerbation rate in individuals treated with a LAMA compared with those treated with a LABA (relative risk [RR] = 0.87, 95% CI, 0.53 to 1.42) as an add-on to an ICS. The exacerbation rate was 4.9 percent (75/1,533) in the LAMA group and 5.4 percent (56/1,041) in the LABA group (absolute risk difference of 7 fewer per 1,000; 95% CI, from 25 fewer to 23 more). The certainty of evidence is moderate for the effect on exacerbations.

Two RCTs[170] in 1,577 patients detected no differences in asthma control between those treated with a LAMA and those treated with a LABA. The certainty of evidence is high for the lack of improvement in asthma control.

Four RCTs[168-170] in 1,982 patients found no differences in asthma-related quality of life between those treated with a LAMA and those treated with a LABA. The certainty of evidence is high for the lack of effect on asthma-related quality of life.

Six RCTs[166,167,169-172] in 2,450 patients found no between-group differences in use of rescue medications. The certainty of evidence is low for the effect on rescue medication use.

Finally, four RCTs[166,167,170] showed no between-group differences in all-cause mortality rates (odds ratio = 7.50, 95% CI, 0.78 to 72.27). The mortality rates were 0.2 percent (3/1,835) in the LAMA group and 0 percent in the LABA group (0/1,135). The certainty of evidence is low for the effect on mortality.

With respect to harms, data from double-blinded, placebo-controlled RCTs suggest a similar rate of undesirable side effects in individuals treated with ICS-LABA and those treated with an ICS plus a LAMA.[166,168-170] However, a real-world comparative effectiveness study[167] that compared the two treatments, the Blacks and Exacerbations on LABA vs. Tiotropium (BELT) study, found a 2.6-fold higher rate of asthma-related hospitalizations in the ICS plus LAMA group than in the ICS-LABA group. In addition, the number of hospitalizations in the ICS plus LAMA group in the BELT study (3.6 per 100 hospitalizations/person/year) was higher than in the ICS-LABA groups in the FDA-required safety studies (0.66 per 100 hospitalizations/person/year).[173] While few asthma-related deaths occurred in BELT (2 of 1,070 participants), both deaths occurred in the ICS plus LAMA group (2/532, 0.38 percent). The proportion of asthma-related deaths in the ICS plus LAMA group in BELT was 38 times higher than the proportion in an ICS-LABA group in the FDA-required safety studies.[173] Because of its real-world effectiveness design, the BELT study might better reflect the harms and benefits likely to occur in clinical practice than efficacy studies of the combination of LAMA and ICS therapy. The BELT study included only Blacks, and no similar data are available from real-world trials that assessed harms in other populations. Therefore, the Expert Panel was unable to determine whether these harms are a concern only in Blacks or whether they might occur in other populations.

The summary of evidence for Recommendation 15 can be found in Appendix B (EtD Table XXI). The Expert Panel compared the harms and benefits of adding a LAMA to ICS therapy with adding a placebo to continued ICS therapy in five RCTs (total N = 3,036).[166,169,170,174,175] These trials showed that adding a LAMA to ICS therapy resulted in a slightly smaller rate of exacerbations, 4.2 percent, than the addition of a placebo to continued ICS therapy, 7.4 percent (absolute risk difference = 24 fewer per 1,000; 95% CI, from 38 fewer to 6 fewer; RR = 0.67; 95% CI, 0.48 to 0.92). According to these results, 42 patients (95% CI, 26 to 167) would need treatment to prevent one exacerbation. This effect on exacerbations has moderate certainty of evidence. However, adding a LAMA to ICS therapy did not improve asthma control (measured by the Asthma Control Questionnaire [ACQ-7, moderate certainty of evidence]).[166,170,174-176] The proportion of responders (those with a ≥0.5 point decrease in score) was 67 percent in the group treated with ICS plus LAMA and was 61 percent in the group treated with placebo added to continued ICS therapy (RR = 1.08; 95% CI, 0.96 to 1.21). In addition, adding a LAMA to an ICS did not improve asthma-related quality of life (measured by the Asthma-Related Quality of Life Questionnaire [AQLQ], high certainty of evidence)[169,170] and had no effect on rescue medication use (high certainty of evidence).[166,170,174-176]

Harms data are available from six studies that compared the efficacy of adding a LAMA to ICS therapy with adding a placebo to ICS therapy.[166,170,174-176] In these studies, the rate of serious adverse events for the addition of a LAMA to ICS therapy was low and was similar to that for the addition of a placebo to ICS therapy. No deaths were reported for any of these studies (see EtD Table XXI). All studies excluded participants with a history of glaucoma or urinary retention. Therefore, whether adding LAMA to ICS therapy is safe in individuals with these conditions is not known.

Rationale and Discussion

Outcomes from seven RCTs[166-172] showed no significant differences between groups. This evidence therefore provides no basis, based on benefits, for recommending the addition of a LAMA to ICS therapy as opposed to the addition of a LABA to ICS therapy in adults with uncontrolled persistent asthma.

The Expert Panel considered the serious adverse events in African-American adults assigned to the ICS plus LAMA group in the BELT study.[167] The number of asthma-related deaths in this group was higher than expected in African-American adults, and the adjusted rate of asthma-related hospitalizations was statistically higher in the ICS plus LAMA group than in the ICS-LABA group. Although it is difficult for the Expert Panel to draw firm conclusions, in the opinion of the Expert Panel, the balance of the evidence argues against adding a LAMA to an ICS compared with adding a LABA to an ICS because

the benefits of added LAMA are trivial, and there is a small concern about the safety of LAMA combined with ICS alone.

In the studies that compared the addition of a LAMA to an ICS with ICS therapy alone, adding a LAMA to an ICS slightly reduced the number of exacerbations[166,169,170,174,175] but did not improve asthma control[166,170,174-176] or asthma-related quality of life.[169,170] The Expert Panel's judgment about the degree of benefit was subjective because no established standards are available for the minimal important difference in exacerbations. In addition, individuals with asthma who place a higher value on asthma control and quality of life than on exacerbations may not perceive any benefit from this intervention.

After considerable discussion about the harms found in the BELT study,[167] the Expert Panel concluded that BELT did not address the harms of adding a LAMA to an ICS compared with adding placebo to ICS therapy.[167] However, because BELT showed a higher adverse event rate in participants assigned to ICS plus LAMA than in those treated with ICS-LABA, the Expert Panel recommends first considering the addition of a LABA to an ICS and considering the addition of a LAMA to an ICS as an alternate approach. This prioritization of therapies may be particularly important in Black adults. The balance of evidence demonstrates that the addition of a LAMA to an ICS offers a small benefit compared with ICS therapy alone, but there is a small concern related to harm.

In addition to the studies described above, the systematic review report compared the efficacy of the addition of a LAMA to ICS controller therapy in individuals ages 12 years and older and adults with uncontrolled, persistent asthma with the efficacy of the addition of montelukast to ICS therapy (EtD Table XXII) and with a doubled ICS dose (EtD Table XXIII).[6] A single small RCT[171,172] produced findings in participants ages 18 to 60 years after 6 months of treatment in a four-arm, parallel-group, unmasked, active-comparator trial (N = 72 for ICS plus LAMA, N = 68 for ICS plus LABA [formoterol], N = 81 for ICS plus montelukast, and N = 76 for ICS plus doxofylline). A total of 297 of the original 362 participants completed the 6-month study. The study report provided no data on *critical* outcomes designated by the Expert Panel. The authors reported on only one of the *important* outcomes (rescue medication use, reported as the difference at day 90 compared with at baseline), and results for this outcome did not differ between groups. In addition, the rate of undesirable effects was similar with both treatments.

After reviewing the available evidence and finding the effect on one noncritical outcome to be inconclusive, the Expert Panel concluded that the data were insufficient to address this question. Therefore, the Expert Panel refrained from making any recommendation regarding the addition of a LAMA to an ICS versus adding montelukast to ICS.

Only one study compared the addition of a LAMA to an ICS with doubling the dose of the ICS. This study found no differences in rates of exacerbations, asthma control, or serious adverse events as well as no differences in asthma-related quality of life between the two groups; no deaths occurred in either group.[168] Although this study showed an improvement in the proportion of control days and in symptom scores of participants assigned to added LAMA treatment, this outcome measure was not validated, and the Expert Panel could not determine the significance of these differences. Therefore, the Expert Panel concluded that the data were insufficient to make a recommendation regarding the addition of a LAMA to an ICS versus doubling the ICS dose.

The Expert Panel also did not make any recommendation regarding the addition of a LAMA to an ICS versus the addition of doxofylline to an ICS because doxofylline is not available in the United States.

Question 5.3

What is the comparative effectiveness of LAMA as add-on therapy to ICS plus long-acting beta$_2$-agonists (LABA) compared with ICS plus LABA as controller therapy in individuals ages 12 years and older with uncontrolled persistent asthma?

Recommendation 16: In individuals ages 12 years 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 recommendation, moderate certainty of evidence

Implementation Guidance

Clinician's Summary:

For individuals whose asthma is not controlled with ICS-LABA, the Expert Panel recommends the addition of a LAMA for many individuals.

- Based on the studies available, the addition of a LAMA to ICS-LABA in individuals ages 12 years and older with uncontrolled persistent asthma offers a small benefit.
- This therapy is recommended for individuals ages 12 years and older whose asthma is uncontrolled even though they are using ICS-LABA therapy.
- LAMA therapy should not be used in individuals with glaucoma or urinary retention.
- Adding a LAMA to ICS-LABA for individuals with uncontrolled asthma who are already taking ICS-LABA improves asthma control and quality of life but has no effect on asthma exacerbations that require systemic corticosteroids or rescue medication.
- **What clinicians should discuss with their patients about adding LAMA therapy to ICS-LABA:**
  - Adding LAMA therapy to ICS-LABA requires the use of an additional and different type of inhaler.
  - The addition of a LAMA may improve asthma control and quality of life but may not decrease the frequency of asthma exacerbations, use of oral corticosteroids, or use of rescue medications.
  - Individuals with glaucoma and those at risk of urinary retention should not use LAMA therapy.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and two *important* outcomes (rescue medication use and mortality). The summary of evidence for Recommendation 16 can be found in evidence to decision table (EtD) Table XXIV in Appendix B.

Two trials (total N = 912) found that the proportion of adults who achieved the minimally important difference (MID) of 0.5 points on the ACQ-7 for asthma control was higher when tiotropium was added to ICS-LABA than when placebo was added (RR = 1.28; 95% CI, 1.13 to 1.46); these studies provided moderate certainty of evidence.[177] The single study (N = 388) in youth ages 12 to 17 years found no difference in the proportion whose ACQ-7 scores improved (RR = 1.01; 95% CI, 0.89 to 1.14).[178] These three studies (total N = 1,301)[177,178] found similar decreases in mean ACQ-7 scores in youths and adults treated with tiotropium and ICS-LABA and in those treated with placebo added to ICS-LABA (mean difference = 0.07 points lower; 95% CI, from 0.31 lower to 0.17 higher); the certainty of evidence is moderate.

Similarly, a higher proportion of adults showed a MID of at least 0.5 points for improved asthma quality of life, as measured by the AQLQ, with the addition of a LAMA to ICS-LABA than with the addition of a placebo to continued ICS-LABA (RR = 1.62; 95% CI, 1.34 to 1.96); the certainty of evidence is high.[177] However, the study did not show a between-group difference in the mean AQLQ score (high certainty of evidence). In addition, three trials (total N = 1,299)[177,178] showed no difference in asthma exacerbations requiring treatment with systemic corticosteroids (RR = 0.84; 95% CI, 0.57 to 1.22; moderate certainty of evidence) or in two trials (N = 907),[177] in exacerbations requiring hospitalization (RR = 0.80; 95% CI 0.42 to 1.52; moderate certainty of evidence). The findings showed no between-group difference in the mean number of puffs of rescue medication in 24 hours (95% CI, 0.37/day less to 0.18/day more; moderate certainty of evidence) or mortality rates (no deaths in either group; very low certainty of evidence).

Rationale and Discussion

In the studies described above, the desirable effects on asthma control and quality of life of the addition of a LAMA to ICS-LABA compared with the addition of placebo were small, and the risks of asthma exacerbations and of adverse events did not differ between the added LAMA and placebo groups. The Expert Panel believes that the balance of outcomes probably favors adding a LAMA to ICS-LABA instead of continuing the same dose of ICS-LABA alone (moderate certainty of evidence). In addition, the Expert Panel does not believe that the extent to which individuals with asthma value the critical outcomes varies or is uncertain. Thus, the addition of a LAMA to ICS-LABA is probably acceptable. However, individuals with asthma and other stakeholders who place less value on asthma control and quality of life than on exacerbations may not find the addition of a LAMA acceptable. Using a LAMA as an add-on therapy is feasible but requires teaching individuals with asthma how to appropriately use devices that deliver the LAMA. The Expert Panel concludes that the use of a LAMA as add-on therapy to ICS-LABA would probably improve health equity because asthma disproportionately affects disadvantaged populations.

The Expert Panel also compared the use of a LAMA as add-on therapy to ICS-LABA with doubling the dose of ICS and continuing the same dose of LABA in individuals ages 12 years and older with uncontrolled persistent asthma (EtD Table XXV). A single, small, open-label RCT randomized 94 individuals who continued to take LABA on a 1:1:1 basis to add-on, once-daily tiotropium bromide 18 mcg; montelukast 10 mg; or double-dose ICS.[179] The data were insufficient to support a judgment about the balance of desirable and undesirable effects. The Expert Panel therefore did not find sufficient data to formulate recommendations about the use of a LAMA as add-on therapy to ICS compared with increasing the dose of ICS and continuing the LABA.

Future Research Opportunities

The Expert Panel offers the following suggestions for future research:

- Comparative effectiveness studies of LAMA therapy for asthma. Because the majority of LAMA studies were efficacy studies, the clinical impact of LAMA treatment in real-world settings is not well understood
- Comparative effectiveness and safety of ICS plus LAMA versus ICS-LABA in ethnically diverse population in studies that are adequately powered to examine the harms and benefits of these two treatment options
- Systematic reviews in children with asthma ages 6–11 years to inform future guidelines
- Comparisons of a LAMA to a leukotriene inhibitor as add-on therapy to ICS-LABA in individuals with uncontrolled persistent asthma
- Role of LAMAs other than tiotropium as add-on therapy to ICS therapy in individuals ages 12 years and older with uncontrolled persistent asthma

SECTION VI

The Role of Subcutaneous & Sublingual Immunotherapy in the Treatment of Allergic Asthma

Background

This section addresses immunotherapy in individuals with allergic asthma. Immunotherapy is the administration of an aeroallergen either subcutaneously (subcutaneous immunotherapy [SCIT]) or sublingually (sublingual immunotherapy [SLIT] in the form of aqueous drops or tablets). The Expert Panel explored the efficacy and safety of the use of both SCIT and SLIT for the treatment of allergic asthma and made two recommendations.

Definition of Terms Used in This Section

"Allergic asthma" refers to asthma that becomes symptomatic after acute exposure to something to which the individual is allergic (e.g., a pet) or during a specific season (e.g., in the spring, when trees shed pollen, or in the fall, when ragweed pollen disperses through the air). In contrast, the term "allergic asthma" is used in many clinical trials to describe a population of children and adults with asthma who show evidence of allergic sensitization based on immediate hypersensitivity skin testing or in vitro serum immunoglobulin E (IgE) testing, regardless of whether they have documented symptoms after relevant exposures. However, more recent trials of immunotherapy have more clearly documented the presence of sensitization and relevant symptoms on exposure to allergens.

"Immunotherapy" (both subcutaneous and sublingual) in this report refers to treatments used to reduce the IgE-mediated allergic clinical response that is associated with asthma. Immunotherapy consists of the therapeutic administration of exogenous aeroallergens to which a person has demonstrable sensitization with the goal of attenuating that individual's asthmatic response on subsequent exposure to these aeroallergens. Immunotherapy can be administered in two ways: subcutaneously by injection (in individuals ages 5 years or older) or sublingually in either liquid or tablet form. The U.S. Food and Drug Administration (FDA) has not approved the use of liquid sublingual immunotherapy or tablet forms of immunotherapy for the specific treatment of asthma, but tablet forms do have FDA approval for treatment of allergic rhinitis and conjunctivitis in individuals ages 5 years and older who have sensitization to northern grass and those ages 18 years and older with sensitization to a short ragweed and dust mite mixture.

Before receiving immunotherapy, individuals with asthma must demonstrate allergic sensitization using one of two methods:

1. Immediate hypersensitivity skin testing followed by an assessment 15—20 minutes later for a wheal and flare reaction to the allergens tested
2. Laboratory testing to measure the level of (aeroallergen) antigen-specific IgE antibody in a blood sample

Question 6.1

What is the efficacy and safety of SCIT?

Recommendation 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 recommendation, moderate certainty of evidence

Implementation Guidance

Clinician's Summary:

The Expert Panel conditionally recommends SCIT as an adjunctive treatment for individuals who have demonstrated allergic sensitization and evidence of worsening asthma symptoms after exposure to the relevant antigen or antigens either acutely (e.g., allergy to pets) or on a seasonal basis (e.g., allergy to grass or ragweed) or a chronic basis (e.g., allergy to dust mites). Individuals who place a high value on possible small improvements in quality of life, symptom control, and a reduction in long-term and/or quick-relief medication use and a lower value on the risk of systemic reactions of wide-ranging severity might consider SCIT as adjunct therapy.

For individuals with allergic asthma, the Expert Panel makes the following suggestions to implement SCIT:

- Clinicians can consider SCIT for adults and children (at a developmental stage at which allergic sensitization can be demonstrated) with allergic asthma, a history compatible with a temporal association of worsening symptoms with exposure to aeroallergens, and testing (as described previously) that confirms this sensitization.

- Clinicians can consider SCIT for individuals whose asthma is not well controlled by their current medical therapy and the treating clinician considers allergen exposure to be a significant contributor to this lack of asthma control. However, clinicians should attempt to optimize asthma control before initiating SCIT to reduce the potential for harm.
- Clinicians can consider SCIT for individuals whose asthma is well controlled by their current therapy when these individuals and/or their clinicians want to reduce the individuals' medication burden.
- In addition to assessing whether an individual with allergic asthma has an appropriate history before considering SCIT, clinicians must formally assess allergic sensitization using either immediate hypersensitivity skin testing or in vitro antigen-specific IgE antibody testing. This evaluation needs to be performed by a trained health care professional skilled in proper testing and result interpretation. The need for these types of specialty evaluations, as with the need for many diagnostic tests and therapeutic interventions, may limit access to care, depending on local availability of these tests and the patient's health insurance coverage of testing.
- Clinicians should not administer SCIT in individuals with severe asthma. Furthermore, clinicians should not initiate, increase, or administer maintenance SCIT doses while individuals have asthma symptoms. These individuals should achieve optimal asthma control before beginning SCIT to minimize the harms (systemic reactions) associated with SCIT, which tend to intensify as baseline asthma severity increases.
- The presence of allergic sensitization is necessary but not sufficient to define the allergic asthma phenotype. A positive test result may not be associated with asthma control over time but might, instead, reflect sensitivity in a different organ (e.g., the nose in allergic rhinitis).
- Allergen exposure could be the only triggering mechanism for allergic asthma symptoms, or it could be just one triggering factor for an individual, and another factor or factors (e.g., respiratory tract infections, irritant exposure, or exercise) might also play a role in triggering allergic asthma symptoms. Because of the heterogeneous nature of allergic asthma, determining the precise efficacy of immunotherapy in reducing the allergic component of an individual's asthma can be difficult.
- Clinicians should administer SCIT in their offices and provide direct supervision because of the risk of systemic reactions. Such reactions can include a range of anaphylactic symptoms involving the skin (urticaria), respiratory tract (rhinitis and asthma), gastrointestinal tract (nausea, diarrhea, and vomiting), and the cardiovascular system (hypotension and arrhythmias). Although rare, deaths after injections have been reported.
- Individuals with asthma should not administer SCIT at home.
- Because clinicians should administer SCIT with direct supervision, personnel with appropriate training should prepare and administer injections for each individual's dosing schedule, from the build-up to the maintenance phase. Equipment and personnel should be available to treat serious anaphylactic reactions.
- One of the potential benefits of SCIT is its immunomodulatory effects, which can reduce the allergic inflammatory response in various tissues.[180,181] Thus, SCIT has the potential to be disease-modifying and to reduce the clinical expression or severity of asthma over time.[181,182]
- Before administering each SCIT injection, clinicians should assess individuals with asthma for worsened asthma symptoms that suggest recent loss of asthma control. Physicians should consider withholding SCIT injections temporarily in patients whose asthma symptoms have worsened until their asthma control is restored.

- **What clinicians should discuss with their patients:**
  - Clinicians should inform individuals with asthma who are considering SCIT that this treatment has the potential to reduce asthma symptoms and the severity of disease over time.
  - Individuals need to come to their doctor's office for SCIT because of the associated risk of systemic reactions.
  - Local and systemic reactions of SCIT include a range of anaphylactic symptoms involving the skin (urticaria), respiratory tract (rhinitis and asthma), gastrointestinal tract (nausea, diarrhea, and vomiting), and the cardiovascular system (hypotension and arrhythmias). Although rare, deaths after injections have been reported.
  - Individuals with asthma should not administer SCIT at home.
  - Before initiating immunotherapy, clinicians must review with the individual who has asthma the travel arrangements and time needed to travel to and from the clinic as well as the requirement for at least a 30-minute observational period after each injection. These requirements may complicate compliance. Missed appointments due to scheduling problems are a safety and an efficacy concern because they may increase the likelihood of local and systemic reactions. Missed appointments can also complicate the ability to reach a maintenance dosing regimen that maximizes therapeutic benefit.
  - Delayed systemic reactions (those occurring more than 30 minutes after injection) occur in approximately 15 percent of individuals after injection.[183]
  - The Expert Panel recommends that individuals who have had previous clinically significant reactions to immunotherapy ideally should have injectable epinephrine and carry it on their person to and from the clinic on the day of their injection.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and three *important* outcomes (use of quick-relief medication, adverse events [harms], and long-term medication use). Because none of the SCIT studies used validated asthma control outcome measures, the Expert Panel used nonvalidated outcome measures (e.g., symptom diaries) as surrogate measures of asthma control when it evaluated 44 studies, but only if the studies used a placebo injection as the comparator.[184-226]

The summary of evidence for Recommendation 17 can be found in evidence to decision (EtD) Table XXVI in Appendix B. Most studies included in the systematic review report evaluated individuals with mild to moderate asthma. The status of asthma control in the studies varied and is classified as controlled, not reported, or uncontrolled. The Expert Panel judged the certainty of evidence for SCIT as low for a small benefit with respect to the *critical* outcomes of exacerbations, quality of life, and asthma control. Studies on exacerbations were limited. One very small study (N = 29) suggested a decrease in exacerbations (very low certainty of evidence).[227] Two studies (N = 119) reported an improvement in quality of life (low certainty of evidence).[187,200] Both studies used a validated outcome measure but scored the individual domains separately. Two other small studies (N = 57) found no difference in quality of life in individuals treated with SCIT or the comparator.[228,229] In the judgment of the Expert Panel, the evidence overall favors SCIT for an improvement in quality of life. Using asthma symptom diaries as a surrogate measure of asthma control, 26 of 44 studies (59 percent) found reductions in severity of symptoms with SCIT in comparison with the placebo

group.[185-189,191,194,199-203,205,207,210-215,217,218,222,223,225,226] Based on these data from studies that used surrogate measures, in the judgment of the Expert Panel, the evidence favors SCIT for an improvement in asthma control (low certainty of evidence).

The Expert Panel noted that when asthma is treated with SCIT, the symptoms of comorbid conditions, such as allergic rhinitis and allergic conjunctivitis, may improve and have a beneficial effect on quality of life.

For the *important* outcomes, SCIT may reduce use of quick-relief medications[214] (low certainty of evidence) and reduce long-term medication use[199,200,214] (moderate certainty of evidence). Reported harms related to SCIT were highly variable, and local reactions around the injection site occurred with 7 to 11 percent of the SCIT doses given.[5] Studies[5] have found systemic reactions with up to 12 percent of total injections, during 0.1 percent of injection visits, and in 80–85 percent of practices. These systemic reactions include pruritus, urticaria, eczema, atopic dermatitis and other forms of eczema, rhinitis, conjunctivitis, nasal congestion, cough, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension.[5] Rates of systemic allergic reactions consistent with anaphylaxis also varied greatly, and randomized controlled trials (RCTs)[5] did not have the statistical power to assess such effects. Poorly controlled asthma is a major risk factor for fatal allergic reactions from SCIT. The incidence of fatal and near-fatal anaphylactic reactions ranges from 1 in 20,000 to 1 in 200,000 injections.[183,230] The incidence of fatal anaphylactic reactions ranges from 1 in 2 million to 1 in 9 million injections[230] (low certainty of evidence because of imprecision).

Rationale and Discussion

Considering the overall balance between benefits and harms, in the judgment of the Expert Panel, the SCIT recommendation is conditional because individuals may consider SCIT as adjunct therapy if they have the following characteristics:

- Place a high value on small improvements in quality of life and symptom control
- Place a high value on reductions in long-term and/or quick-relief medication use
- Place a lower value on the potential for systemic reactions of wide-ranging severity

The studies available for evaluation tended to have small samples, and study reports did not characterize the races of participants or the social determinants of health that they experienced.[5] Studies of SCIT used different protocols and did not use standardized formulations or have a uniform or standardized duration of follow-up. The efficacy of SCIT, which has an acceptable burden of harms, is based on its impact on asthma quality of life and asthma-related symptoms, with low certainty of evidence. Whether to use SCIT should be a shared decision between the individual and the health care provider, and this decision should consider the individual's asthma severity and willingness to accept the potential harms related to SCIT. Clinicians should administer SCIT in a clinical setting that has the capacity to monitor and treat reactions.

The enthusiasm of the Expert Panel for recommending SCIT for allergic asthma management is reduced by the slight risk of harms and variability in access (because of costs and geographical location); this variability in access can promote health inequities.

Question 6.2

What is the efficacy and safety of SLIT?

Recommendation 18: In individuals with persistent allergic asthma, the Expert Panel conditionally recommends against the use of sublingual immunotherapy in asthma treatment.

Conditional recommendation, moderate certainty of evidence

Implementation Guidance

Clinician's Summary:

The evidence that the Expert Panel reviewed did not support the use of SLIT specifically for the treatment of allergic asthma. However, the FDA has approved SLIT tablets (but not aqueous preparations) for the treatment of allergic rhinoconjunctivitis. Individuals with this condition who also have asthma might benefit from SLIT and, if so, this benefit is most likely to be in the form of a reduction in the use of quick-relief and/or long-term control medications.

On the basis of the currently available data, the Expert Panel does not recommend SLIT for allergic asthma. SLIT is beneficial for allergic rhinoconjunctivitis.[231] In an individual with comorbid allergic asthma, SLIT for allergic rhinoconjunctivitis might reduce the symptoms of allergic asthma as well (and this potential provides the rationale for making the recommendation conditional). For individuals whose allergic asthma symptoms benefit from SLIT for allergic rhinoconjunctivitis, the Expert Panel offers the following suggestions.

- The clinician should administer the first dose of SLIT in the office, and the individual with asthma should wait in the office for at least 30 minutes after receiving the dose. If no problems develop, the individual may continue the SLIT dosing at home. Individuals receiving SLIT should ideally have an injectable epinephrine prescription and receive education on how to administer this medication.
- Currently, only tablet SLIT formulations for short ragweed and dust mite mixture and for northern grass have FDA approval for treatment of allergic rhinitis with and without conjunctivitis. SLIT is not FDA approved specifically for asthma treatment.
- **What clinicians should discuss with their patients:**
  - The Expert Panel does not recommend SLIT for the treatment of allergic asthma, but this treatment may benefit individuals with certain comorbid conditions, such as allergic rhinitis with or without conjunctivitis.
  - The FDA has approved the use of SLIT to treat allergic rhinitis and conjunctivitis in response to only a few allergens at this time for individuals ages 5 years and older (for sensitization to northern grass) and in individuals ages 18 years and older (for sensitization to a short ragweed and dust mite mixture).

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and three *important* outcomes (quick relief medication, adverse events [harms], and long-term medication use). The summary of evidence for Recommendation 18 can be found in EtD Table XXVII in Appendix B.

The evidence shows that SLIT provides a trivial benefit for the *critical* outcomes of exacerbations,[232,233] asthma control,[234-239] and quality of life[232-234,237,238] (moderate certainty of evidence). No studies assessed the impact of SLIT on emergency department visits, clinic visits, or hospitalizations. Three studies evaluated exacerbations using different endpoints. One study did not report the number of exacerbations, but it did report on the time to first exacerbation.[233] SLIT decreased the severity of the first moderate exacerbation, but it did not increase the time to first severe exacerbations requiring systemic corticosteroids. Another study did not provide any raw data or rates of the critical outcomes, and the authors only noted that the results showed no statistically significant improvement in asthma exacerbations.[234,237,238] The third study, which enrolled only 60 participants, found a significantly lower number of exacerbations in the treatment group.[232] Four studies (N = 1,193) that evaluated asthma control using validated outcome tools (three used the Asthma Control Questionnaire, and one used the Asthma Control Test) found no consistent improvement after treatment.[233-239] Finally, multiple studies showed no difference in quality of life in those treated with SLIT or placebo[233-235,237-239] (high certainty of evidence).

For important outcomes, SLIT reduced the use of quick-relief medications[232,236,240-242] and doses of inhaled corticosteroids,[234,235,242,243] with moderate certainty of evidence.

The harms were difficult for the Expert Panel to evaluate. Local reactions were frequent and occurred in up to 80 percent of individuals treated with SLIT, but adverse local reactions were also common in those receiving placebo. The rate of side effects did not differ by the setting of administration (home, clinic, or other), and the relationship between the risk of side effects and the strength of the dose administered was not consistent across studies. None of the RCTs (N = 1,772)[233,234,243-246] reported episodes of anaphylaxis. The Expert Panel found no reports of death that was secondary to SLIT.

Rationale and Discussion

The 2014—2015 needs assessment report by the National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group[2] included both aqueous and tablet formulations in the research questions on the efficacy and safety of SLIT. For these questions, the systematic review report combined studies of the two types of SLIT, thereby increasing the sample sizes and precision of results for many of the outcomes evaluated.[12] However, the designs and methodologies of RCTs that used aqueous and drop preparations of SLIT were not as rigorous or standardized as they were for studies that used tablet formulations. In evaluating the data on aqueous or drop and tablet formulations combined, the Expert Panel did not find that SLIT reduced asthma symptoms or improved asthma control or asthma quality of life. Although systemic side effects were common (80 percent of participants), they were also common in the placebo groups.[5] In addition, the limited number of FDA-approved antigens, the costs of SLIT, and the variability in access to this treatment promote health inequities.

Overall Summary for SCIT and SLIT

The Expert Panel conditionally recommends SCIT as an adjunct treatment to standard pharmacotherapy for individuals ages 5 years and older with mild to moderate persistent asthma who show clear evidence of a relationship between symptoms and exposure to an allergen to which the individual is sensitive.[12] The Expert Panel conditionally recommends against the use of SLIT as a treatment specifically for asthma.

The Expert Panel's immunotherapy recommendations call for shared decision-making between the clinician and the individual with asthma. The recommendations also highlight SLIT's potential to reduce the symptoms of comorbid conditions, such as allergic rhinitis and allergic conjunctivitis, and this potential improvement may be an important consideration for individuals with allergic asthma.[5]

Future Research Opportunities

The Expert Panel identified the following opportunities for additional research:

- Investigate the safety and efficacy of immunotherapy in individuals with severe asthma, particularly those whose asthma is under control but who want to reduce their medication burden
- Include only children ages 5–11 years in studies of children, or, if a study includes a broader age group, report findings separately for children ages 5–11 years and those ages 12 years and older
- Study more diverse populations to determine whether race or ethnicity influences the efficacy and safety of immunotherapy
- Study the efficacy and safety of multiple-allergen SCIT or SLIT regimens to assess compliance, adherence, and the effect of these factors on asthma management
- Standardize methods to report SCIT and SLIT doses used in studies and use validated outcome measurement instruments, such as asthma symptoms and adverse events

SECTION VII

Recommendations for the Use of Bronchial Thermoplasty to Improve Asthma Outcomes

Background

The Expert Panel examined studies that compared bronchial thermoplasty (BT) to multicomponent, standard-of-care, medical management and to sham bronchoscopy plus multicomponent medical management. BT is an asthma intervention that was developed over the last decade and was not addressed in previous versions of the asthma guidelines. The Expert Panel made one recommendation on the use of BT for asthma treatment.

Definitions of Terms Used in this Section

Multicomponent medical therapy consists of medium to high doses of inhaled corticosteroid (ICS) treatment, long-acting beta$_2$-agonists (LABAs), omalizumab (in one study), and/or oral corticosteroids. Available studies of BT did not include individuals treated with long-acting muscarinic antagonists, environmental interventions, and/or newer biologic agents.[247-249]

"Life-threatening asthma" is defined as asthma that has resulted in hospitalization in an intensive care unit and/or has been treated with noninvasive ventilation or intubation in the past 5 years.

Question 7.1

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?

Recommendation 19: In individuals ages 18 years and older with persistent asthma, the Expert Panel conditionally recommends against bronchial thermoplasty.

Conditional recommendation, low certainty of evidence

Individuals ages 18 years and older with persistent asthma who place a low value on harms (i.e., short-term worsening of symptoms and unknown long-term side effects) and a high value on potential benefits (i.e., improvement in quality of life and a small reduction in number of exacerbations) might consider BT.

Implementation Guidance

Clinician's Summary:

Most individuals ages 18 years and older with uncontrolled, moderate-to-severe, persistent asthma should not undergo BT to treat asthma because the benefits are small, the risks are moderate, and the long-term outcomes are uncertain. Some individuals with moderate-to-severe persistent asthma who have troublesome symptoms may be willing to accept the risks of BT and, therefore, might choose this intervention after shared decision-making with their health care provider. Clinicians should offer the procedure in the setting of a clinical trial or a registry study to enable the collection of long-term data on the use of BT for asthma.

The Expert Panel does not recommend BT for individuals ages 18 years and older as part of routine asthma care, even if these individuals have uncontrolled asthma despite using multicomponent medical therapy, because of the small benefit-to-risk ratio. The risks of BT include asthma exacerbations, hemoptysis, and atelectasis during the treatment period. Recognizing, however, that BT is currently being used, the Expert Panel offers the following suggestions for its safe use:

- BT should not be used in individuals with low lung function (forced expiratory volume in 1 second that is less than 50 or 60 percent predicted) and life-threatening asthma.
- BT has not been studied in individuals younger than age 18 years.
- In the opinion of the Expert Panel, when BT is implemented, it should be used in settings that enroll participants in registries, ongoing clinical trials, or studies that track BT's long-term safety and effectiveness.
- For individuals who decide to undergo BT, an experienced specialist (e.g., a pulmonologist with training in BT administration) should provide this treatment in a center that has appropriate expertise.
- Clinicians should optimize asthma treatment and address comorbidities, and they should assess and optimize adherence to existing therapy, before considering BT.
- In some individuals, BT may provide a small benefit that might last 5 years or longer.[250,251]
- BT may reduce severe asthma exacerbations in comparison to standard care after treatment.
- Risks associated with BT include worsening of asthma, respiratory infections, hemoptysis, bronchiectasis, and pulmonary artery complications.[252-254]

- Severe latent or delayed-onset complications have not been reported with BT, but the number of individuals with asthma included in long-term follow-up assessments is very small (fewer than 250 people at the time the systematic review report[3] on this topic was completed).
- **What clinicians should discuss with their patients about BT:**
  - This procedure may reduce severe asthma exacerbations compared with standard care after treatment. Although the benefits could last 5 years or more, only limited data demonstrate that this treatment improves long-term asthma outcomes.
  - The risks associated with BT include worsening of asthma, respiratory infections, hemoptysis, bronchiectasis, and pulmonary artery complications.[252-254] In addition, severe, delayed-onset complications could occur that have not yet been recognized because of the small numbers of individuals who have undergone the procedure.
  - Individuals ages 18 years and older with persistent asthma who place a low value on the harms (short-term worsening symptoms and unknown long-term side effects) and a high value on the potential benefits (improvement in asthma quality of life, small reduction in exacerbations) of BT might consider this treatment.

Summary of the Evidence

The Expert Panel specified three *critical* outcomes (exacerbations, asthma control, and quality of life) and one *important* outcome (use of rescue medication) for this question. The summary of evidence for Recommendation 19 can be found in Appendix B (evidence to decision Table XXVIII).

The conditional recommendation against the use of BT in individuals ages 18 years and older with poorly controlled asthma after medium-to-high-dose ICS treatment paired with a LABA (with or without oral corticosteroids) is based on three randomized controlled trials (RCTs).[247-249] All of these trials were funded by the company that markets the BT device.

Two of the studies compared BT with standard care.[248,249] The Research In Severe Asthma (RISA) study (N = 32)[249] enrolled individuals treated with a high-dose ICS (more than 750 mcg fluticasone or equivalent) and a LABA (100 mcg salmeterol equivalent) with or without daily oral corticosteroids (less than 30 mg/day prednisone equivalent). The Asthma Intervention Research (AIR)[248] study (N = 112) enrolled individuals taking an ICS (more than 200 mcg/day beclomethasone equivalent) and a LABA (100 mcg salmeterol or equivalent). These two studies found improvements in *critical* outcomes, including decreases in numbers of mild exacerbations not requiring oral or parenteral corticosteroids and in numbers of emergency department visits. The results also showed improved asthma control based on Asthma Control Questionnaire scores and less rescue medication use (an *important* outcome).[248,249]

A third study, AIR 2 (N = 288), compared BT with sham bronchoscopy plus standard care.[247] This study enrolled individuals treated with high-dose ICS (more than 1,000 mcg betamethasone or equivalent) plus a LABA. Participants could also continue using leukotriene modifiers and omalizumab if they had used these treatments for at least 1 year. This study found reductions in severe exacerbations requiring oral or parenteral corticosteroid treatment over 12 months in participants treated with BT. Other *critical* outcomes—such as asthma control, mean asthma quality of life scores (measured with the Asthma Quality of Life Questionnaire), and rescue medication use (an *important* outcome)—did not improve. The percentage of participants with Asthma Quality of Life Questionnaire scores of 0.5 or higher (minimally important difference) in the BT group (79 percent) was significantly different from the corresponding proportion (64 percent) in the control (sham bronchoscopy) group. The strength of evidence was low for all of these outcomes across the three studies. None of the studies found that BT reduced the number of hospitalizations for asthma over 12 months.[247-249]

The AIR extension study followed 69 individuals (45 treated with BT and 24 with control treatment) for 3 years.[250] The results did not demonstrate any differences in rates of asthma-related events between the two groups over the additional 24 months.

The RISA[249] and AIR[248] studies found increased rates of bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing during the 12-week BT treatment period. The AIR 2 extension study followed 162 of 190 participants treated with BT for up to 5 years after BT treatment.[251] Long term results from the RISA extension[255] and AIR extension[250] showed ongoing or new dyspnea (9.5 percent of participants), chest discomfort (4.8 to 8.3 percent), bronchial irritation (2.4 percent), wheezing (4.8 to 8.3 percent), and cough (4.8 percent) at the end of the 5-year study period. Hospitalizations during and after the treatment period were more frequent in patients treated with BT in all three studies.[247-249] In the AIR 2 study, 16 of 190 patients treated with BT and 2 of 98 patients in the control group were hospitalized during the treatment period. Ten of the 16 patient hospitalizations in patients treated with BT and both of the hospitalizations of patients in the control group were for worsening asthma. In the RISA study, 4 of 15 patients were hospitalized seven times during the 12 months after treatment, whereas none of the 17 patients in the standard care arm was hospitalized.[248] In addition to being hospitalized for worsening asthma, participants in the BT arms of the three studies were hospitalized for segmental atelectasis, lower respiratory tract infections, low forced expiratory volume in 1 second, hemoptysis, and an aspirated prosthetic tooth.[247-249]

Twelve case reports and small case series reports[252-254,256-264] also described adverse events, including hemoptysis in seven patients, atelectasis in six patients, and lower respiratory tract infections in three patients. One individual in these reports developed a mediastinal hematoma and bloody pleural effusion while on anticoagulation therapy for a pulmonary embolism. The authors of this case report believed that this effect resulted from a pseudoaneurysm of the pulmonary artery caused by the BT. Complications from case reports with one reported occurrence included a lung abscess, an inflammatory bronchial polyp, a pulmonary cyst, and a case of bronchiectasis.[252-254,256-264]

None of the 15 studies reviewed (3 RCTs and 12 case reports and case series) attributed any deaths to BT.

Rationale and Discussion

The data on the benefits and harms of BT derive primarily from three RCTs that enrolled a total of 432 patients in both the intervention and treatment arms. Overall, the improvements after BT were small, and the harms of BT were moderate. Long-term follow-up of a sufficient number of patients to fully assess clinical benefits and harms is lacking. The therapy may offer an acceptable benefit-to- harm ratio for some patients after careful shared decision-making. Further research that includes randomized trials as well as long-term registry outcomes are desirable.

Future Research Opportunities

The Expert Panel identified the following research gaps:

- Identify the population most likely to benefit from BT, such as individuals who have been treated unsuccessfully with different biologic agents
- Develop a registry to determine the risk of significant but rare long-term harms, such as bronchiectasis, vascular damage, and other lung complications. Follow both treated and untreated individuals over the long term to determine whether side effects reported at 5 years in the AIR 2 study[247] are more common in individuals treated with BT than in a control group
- Conduct RCTs and long-term registry studies of BT for asthma treatment, with appropriate controls and a sufficient number of patients, to fully assess the clinical benefits and harms of BT

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APPENDIX A

Key Differences from the Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma

For each of the topics and associated recommendations included in the Selected Updates 2020, this table provides a concise summary of the pertinent recommendations on the same topic that were included in *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3; 2007).[1] For additional information on these and other topics in EPR-3, please refer to the appropriate sections of each document. Fractional exhaled nitric oxide, long-acting muscarinic antagonists, and bronchial thermoplasty were not addressed in EPR-3 and are therefore not listed below.

Key Differences in Recommendations in the 2007 (EPR-3) and 2020 Asthma Guidelines, by Topic Area

TOPIC AREA	2007 GUIDELINE	2020 GUIDELINE
Allergen Mitigation	Patients who have asthma at any level of severity should reduce, if possible, exposure to allergens to which the patient is sensitized and exposed	Conditional recommendation against allergen mitigation interventions as part of routine asthma management 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 **(Recommendation 5)**
	Patients who have asthma at any level of severity should know that effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A)	Conditional recommendation for a multicomponent allergen-specific mitigation intervention in individuals with asthma who are exposed and have symptoms related to exposure to identified indoor allergens, confirmed by history taking or allergy testing **(Recommendation 6)**
	Recommended cockroach control measures if the patient is sensitive to cockroaches and the home has an infestation	Conditional recommendation for the use of integrated pest management alone or as part of a multicomponent allergen-specific mitigation intervention in individuals with asthma who are exposed and have sensitization or symptoms related to exposure to pests (cockroaches and rodents) **(Recommendation 7)**
	Recommended the following mite-control measures: ▪ Encase mattress in an allergen-impermeable cover ▪ Encase pillow in an allergen-impermeable cover or wash pillow weekly ▪ Wash sheets and blankets weekly in hot water	Conditional recommendation for impermeable pillow/mattress covers only as part of a multicomponent allergen mitigation intervention, not as a single-component intervention, in individuals with asthma who have sensitization or symptoms related to exposure to dust mites **(Recommendation 8)**

Key Differences in Recommendations in the 2007 (EPR-3) and 2020 Asthma Guidelines, by Topic Area (cont'd)

TOPIC AREA	2007 GUIDELINE	2020 GUIDELINE
ICS	Recommended following actions for managing acute exacerbations due to viral respiratory infections in children ages 0–4 years: ▪ For mild symptoms: SABA every 4–6 hours for 24 hours or longer with a physician consult ▪ For moderate to severe exacerbations, consider a short course of oral systemic steroids	Conditional recommendation for starting a short course of daily ICS at the onset of a respiratory tract infection with PRN SABA for quick-relief therapy in children ages 0–4 years with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections (Step 1) **(Recommendation 9)**
	Recommended daily low-dose ICS+PRN SABA for individuals ages 12 years and older with mild persistent asthma (Step 2)	Conditional recommendation for either daily low-dose ICS and PRN SABA for quick-relief therapy or ICS and SABA used concomitantly PRN for individuals ages 12 years and older with mild persistent asthma (Step 2) **(Recommendation 10)**
	Recommended daily medium-dose ICS + PRN SABA *or* low-dose ICS/LABA + PRN SABA for individuals ages 12 years and older with moderate persistent asthma (Step 3) Recommended daily medium-dose ICS/LABA + SABA for quick-relief therapy in individuals ages 5 years and older with moderate to severe persistent asthma (Step 4)	Conditional recommendation against a short-term increase in ICS dose (e.g., doubled dose) for increased symptoms or decreased peak flow in individuals ages 4 years and older with mild to moderate persistent asthma who are on daily ICS treatment and likely to be adherent to this therapy **(Recommendation 11)** Strong recommendation for ICS-formoterol in a single inhaler 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 in individuals ages 4 years and older with moderate to severe persistent asthma (Step 3 for low-dose ICS and Step 4 for medium-dose ICS) **(Recommendation 12)** Conditional recommendation for 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 in individuals ages 12 years and older with moderate to severe persistent asthma (Step 4) **(Recommendation 13)**

Key Differences in Recommendations in the 2007 (EPR-3) and 2020 Asthma Guidelines, by Topic Area (cont'd)		
TOPIC AREA	**2007 GUIDELINE**	**2020 GUIDELINE**
Immunotherapy	Consider allergen immunotherapy for persistent asthma in the presence of symptoms and sensitization (one combined recommendation)	Conditional recommendation for use of SCIT as an adjunct treatment to standard pharmacotherapy in individuals ages 5 years and older with mild to moderate allergic asthma whose asthma is under control at the initiation, build-up, and maintenance phases of immunotherapy **(Recommendation 17)** Conditional recommendation against use of SLIT for asthma treatment in individuals with persistent allergic asthma **(Recommendation 18)**

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; PRN, as needed; SABA, short-acting beta$_2$-agonist; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Reference

[1]National Asthma Education and Prevention Program. Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, Maryland: National Heart, Lung, and Blood Institute, National Institutes of Health. Aug. 2007. 440 pp. https://www.ncbi.nlm.nih.gov/books/NBK7232/.

APPENDIX B

Evidence to Decision Tables

Introduction

The Expert Panel used the following Agency for Healthcare Research and Quality (AHRQ) systematic review reports in developing the evidence to decision (EtD) tables. Section I of this report describes in detail the methods used by the Expert Panel to assess the evidence and to create these tables.

EtD Tables I–III:	The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management[1]
EtD Tables IV–XII:	Effectiveness of Indoor Allergen Mitigation in Management of Asthma[2]
EtD Tables XIII–XXV:	Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma[3]
EtD Tables XXVI–XXVII:	The Role of Immunotherapy in the Treatment of Asthma[4]
EtD Table XXVIII:	Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma[5]

Footnotes in all EtD tables provide detailed explanations about the Expert Panel's judgments. When the Expert Panel made a contextualized judgment for a specific outcome (and the judgment of the Expert Panel differed from the judgment made by the Evidence-Based Practice Center as reflected in the AHRQ systematic review report), the report uses the words, "The Expert Panel rated this outcome down for… ." Otherwise, the certainty of evidence and risk of bias ratings reflect the judgments from the published AHRQ systematic review reports, and these ratings are denoted by statements that begin with, "The AHRQ systematic review report rated this outcome down for… ."

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1. Wang Z, Pianosi P, Keogh K, Zaiem F, Alsawas M, Alahdab F, et al. The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management. Comparative Effectiveness Review No. 197. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I). AHRQ Publication No.17(18)-EHC030-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2017. https://doi.org/10.23970/AHRQEPCCER197
2. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Schoelles K, Umscheid C. Effectiveness of Indoor Allergen Reduction in Management of Asthma. Comparative Effectiveness Review No. 201. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-0005-I). AHRQ Publication No. 18-EHC002-EF. Rockville, MD: Agency for Healthcare Research and Quality. February 2018. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER201
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4. Lin SY, Azar A, Suarez-Cuervo C, Diette GB, Brigham E, Rice J, et al. The Role of Immunotherapy in the Treatment of Asthma. Comparative Effectiveness Review No. 196. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No.290-2015-00006-I). AHRQ Publication No. 17(18)-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2018. Posted final reports are located on the Effective Health Care Program search page. DOI: https://doi.org/10.23970/AHRQEPCCER196
5. D'Anci KE, Lynch MP, Leas BF, Apter AJ, Bryant-Stephens T, Kaczmarek JL, et al. Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma. Comparative Effective Review No. 202. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-00005-I). AHRQ Publication No. 18-EHC0003-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2017. https://doi.org/10.23970/AHRQEPCCER202

Evidence to Decision Table I — Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Measurement in Asthma Management in Individuals Ages 5 Years and Older

Background

The Expert Panel recognizes that there is no gold standard for the diagnosis of asthma. Proper diagnosis depends on the amalgam of clinical findings, history, objective measures, and clinical course over time. The choice of assessment methods must take into account test availability, cost, and patient-specific factors. This table summarizes the evidence on FeNO measurement in individuals (children and adults) with symptoms suggestive of asthma (e.g., wheezing or coughing).
FeNO measurement is an add-on test that is part of the workup and evaluation for asthma, with a cutoff value less than 20 ppb.
This evidence addresses Key Question 1a in the systematic review and Question 2.1 in Section II of this report: What is the diagnostic accuracy of fractional exhaled nitric oxide (FeNO) measurement(s) for making the diagnosis of asthma in individuals ages 5 years and older?

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Moderate	When the test is performed in a population with a high pretest probability of asthma (assumed prevalence of 60%), of 1,000 patients who are assessed with FeNO as an add-on test: ▪ TP rate: 474 (95% CI, 426 to 516) individuals will be correctly diagnosed as having asthma. ▪ TN rate: 288 (95% CI, 236 to 324) individuals will be correctly diagnosed as not having asthma. ▪ FP rate: 112 (95% CI, 76 to 164) individuals will be incorrectly diagnosed as having asthma. ▪ FN rate: 126 (95% CI, 84 to 174) individuals will be incorrectly diagnosed as not having asthma.	Individuals who are correctly diagnosed as having asthma (TP result) will benefit from timely treatment. Individuals who are correctly diagnosed as not having asthma (TN result) may be evaluated for other conditions that might contribute to their symptoms.

Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know	There is no reported evidence of direct harms from FeNO testing. If the test is performed in a population with a high pretest probability of asthma (assumed prevalence of 60%), of 1,000 patients assessed with FeNO as an add-on test: ▪ TP rate: 474 (95% CI, 426 to 516) individuals will be correctly diagnosed as having asthma. ▪ TN rate: 288 (95% CI, 236 to 324) individuals will be correctly diagnosed as not having asthma. ▪ FP rate: 112 (95% CI, 76 to 164) individuals will be incorrectly diagnosed as having asthma. ▪ FN rate: 126 (95% CI, 84 to 174) individuals will be incorrectly diagnosed as not having asthma.	Individuals who are incorrectly diagnosed as having asthma (FP result) may experience labeling bias or harm from undergoing treatment with medications (and from their side effects and costs). This unnecessary treatment could lead to a delay in the diagnosis of one or more other conditions that might cause the symptoms being evaluated. Individuals who are incorrectly diagnosed as not having asthma (FN result) may undergo delays in receiving timely treatment and have more exacerbations, worsening symptoms, or a reduced quality of life. See tree diagrams at the end of this set of EtD tables for details.

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Moderate		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Possibly important uncertainty or variability	No research evidence was found on the variability in values of individuals with asthma. The Expert Panel's judgment is that patient values may vary widely with respect to the outcomes and burdens of FeNO testing, including costs and access.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Favors the intervention		

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Little research has been done on this topic. The Expert Panel's judgment is that the intervention would be acceptable to most individuals with asthma because of the ease of undergoing this test.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Few, if any, studies of FeNO testing have been done in primary care settings. FeNO equipment and cost per test may limit the test's use. The use of FeNO testing in many specialists' offices suggests that testing in these settings is feasible and is already conducted in practice.	After a review of the costs and logistics of testing, the opinion of the Expert Panel is that FeNO testing would have limited use in primary care. However, it might be used more frequently in the collaborative care models of some health care systems.

Equity: What would be the impact on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	Evidence is limited on the impact of FeNO testing on health equity. If FeNO testing is used in specialty settings only and coverage or access to specialty care is limited (e.g., because Medicaid does not cover this care), access to this test may not be equal. Whether individuals with asthma have access to FeNO testing may depend on whether the individual's health care insurance plan covers FeNO testing.	Guidelines can influence insurance coverage decisions, and the clinical policies of insurers and federal and state agencies should be based on the evidence for FeNO testing and ensure access to appropriate asthma diagnostic and monitoring services.

Abbreviations: CI, confidence interval; EtD, evidence to decision; FeNO, fractional exhaled nitric oxide; false-negative, FN; false-positive, FP; true-negative, TN; true-positive, TP.

Evidence Summary: Use of Add-on Fractional Exhaled Nitric Oxide Measurement Testing to Diagnose Asthma in Individuals Ages 5 Years and Older (at a Cutoff Level of 20 ppb)

Test	Per 1,000 individuals tested (95% CI)[a]		Number of participants (number of studies)[b]	Certainty of the evidence (using GRADE)	Comments
	Assumed prevalence of 60%	Assumed prevalence of 80%			
True-positive results	474 (426 to 516)	632 (568 to 688)	4,129 (21)	Moderate[c]	These individuals would be correctly diagnosed with asthma and would receive necessary and timely treatment.
False-negative results	126 (84 to 174)	168 (112 to 232)			These individuals would not receive timely treatment, and the lack of timely treatment could lead to more exacerbations, worsening symptoms, and a reduction in quality of life in the short term.
True-negative results	288 (236 to 324)	144 (118 to 162)	4,129 (21)	Moderate[c]	These individuals would be correctly diagnosed as not having asthma and could then undergo testing or evaluation for other suspected diagnoses.
False-positive results	112 (76 to 164)	56 (38 to 82)			These individuals would be incorrectly diagnosed as having asthma and would start taking medications, which could be associated with burdens, adverse effects, and costs. A false-positive test result could also lead to delays in receiving the correct diagnosis.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Footnotes, including GRADE explanations

a. The pooled sensitivity was 0.79 (95% CI, 0.71 to 0.86), and the pooled specificity was 0.72 (95% CI, 0.59 to 0.81). All 21 studies were observational (total N = 4,129); some studies used a diagnosis gold standard of clinical diagnosis only, positive bronchial challenge testing only, or a combination of clinical diagnosis, bronchial challenge, and/or bronchodilator response.

b. The Expert Panel used two estimates of asthma prevalence rates, 60% and 80%, in the population for which add-on FeNO testing was used for diagnosis. These estimates came from clinical experts in a specialty setting who routinely perform diagnostic FeNO testing in individuals referred from primary care practices.

c. The Agency for Healthcare Research and Quality systematic review report rated the certainty of evidence down to moderate for risk of bias because the extent of bias was unclear or high in half of the individual studies.

Evidence Summary: FeNO test characteristics at a cutoff level of less than 20 ppb (subgroup analyses)

Population	Reference test	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Certainty of evidence
Healthy and symptomatic individuals	All available studies regardless of reference test	21 observational studies[1-21]	0.79 (0.71 to 0.86)	0.72 (0.59 to 0.81)	Moderate
Symptomatic individuals without a known diagnosis of asthma	All available studies regardless of reference test	9 studies[a]	0.73 (0.60 to 0.83)	0.62 (0.45 to 0.77)	Not reported
Nonsmokers	All available studies regardless of reference test	17 studies[a]	0.70 (0.61 to 0.78)	0.80 (0.74 to 0.85)	Not reported
Individuals with asthma not previously treated with corticosteroids	All available studies regardless of reference test	6 studies[a]	0.79 (0.67 to 0.87)	0.77 (0.56 to 0.90)	Not reported
Individuals with asthma and atopy	All available studies regardless of reference test	4 studies[a]	0.63 (0.43 to 0.80)	0.79 (0.65 to 0.89)	Not reported

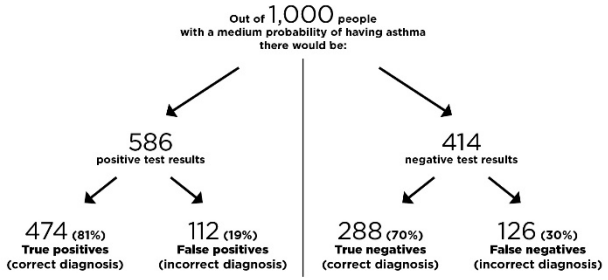
Abbreviations: CI, confidence interval.

Footnotes, including GRADE explanations

a. Publications not included in the Agency for Healthcare Research and Quality systematic review report.

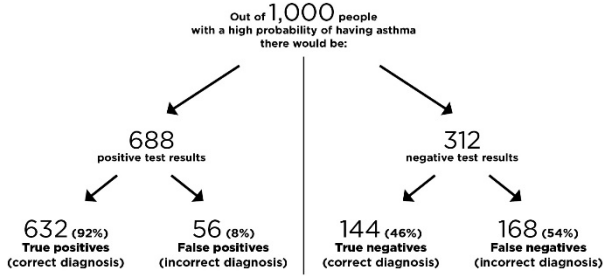
FeNO Diagnostic Accuracy With a **60%** Pretest Probability of Asthma

Pretest Probability of having asthma	Post-test Probability of a person having asthma with test results: with POSITIVE test result	Post-test Probability of a person having asthma with test results: with NEGATIVE test result	Certainty of the evidence (GRADE)
60% of the people in this risk group have asthma	81% of people with a positive test result have asthma (95% CI: 72% to 87%)	30% of people with a negative test result have asthma (95% CI: 21% to 42%)	Moderate



FeNO Diagnostic Accuracy With an **80%** Pretest Probability of Asthma

Pretest Probability of having asthma	Post-test Probability of a person having asthma with test results: with POSITIVE test result	Post-test Probability of a person having asthma with test results: with NEGATIVE test result	Certainty of the evidence (GRADE)
80% of the people in this risk group have asthma	92% of people with a positive test result have asthma (95% CI: 87% to 95%)	54% of people with a negative test result have asthma (95% CI: 41% to 66%)	Moderate



Harms: There were no reported direct harms from FeNO testing.

New evidence

Yes.[22,23]

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Evidence to Decision Table II — Asthma Management Strategy That Includes Fractional Exhaled Nitric Oxide Testing vs. Usual or Standard Care That Does Not Include This Testing

Background

This table compares an asthma management strategy that includes FeNO testing with usual or standard care that does not include FeNO testing. The FeNO-based asthma management strategies in the literature used FeNO measurements in conjunction with other assessments (e.g., forced expiratory volume in 1 second, symptom frequency, Asthma Control Test, or Asthma Control Questionnaire scores) and used beta-agonist treatment to adjust therapy. Because of this heterogeneity in approach, the Expert Panel could not identify a FeNO-based asthma management strategy that is clearly superior to other management strategies. In addition, no established FeNO cutpoints are available for choosing, monitoring, or adjusting anti-inflammatory therapies.
This evidence addresses Key Questions 1c and 1d in the systematic review and Questions 2.2 and 2.3 in Section II of this report:

- 1c and 2.2: What is the clinical utility of FeNO measurements to select medication options (including corticosteroids) for individuals ages 5 years and older?
- 1d and 2.3: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 years and older? The unique code for this document is 898140

Desirable effects: How substantial are the desirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Moderate	FeNO-based strategies reduced exacerbations based on 6 randomized controlled trials in 1,536 adults with asthma. However, the strategies had no impact on quality of life or asthma control.	

Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Trivial	We could find no reports of direct harms from FeNO testing.	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Possibly important uncertainty or variability	No research evidence is available on the variability in the values of individuals with asthma. In the Expert Panel's judgment, there is possibly important variability in values because some individuals with asthma may value quality of life or asthma control more than exacerbations. These values could vary by race or ethnicity and by asthma severity. As a result of these different values, different individuals with asthma might make different choices about an asthma intervention. Also, the burden of FeNO testing might differ because of variations in costs and access for different individuals with asthma.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Favors the intervention	The direct harms of FeNO testing are trivial.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Little research has been reported on asthma management strategies that include FeNO testing.	The Expert Panel believes that the intervention would be acceptable to many individuals with asthma because of the ease of FeNO testing and the benefits of preventing exacerbations.

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Few, if any studies, of FeNO testing have been conducted in primary care settings. The costs of FeNO equipment and FeNO tests may limit the test's use.	The existing use of FeNO in many specialists' offices suggests that testing in these settings is feasible and already done in practice. After a review of the costs and logistics of FeNO testing, the opinion of the Expert Panel is that the intervention would have limited use in primary care settings, although its use might be more common in the collaborative care models of some health care systems.

Equity: What would be the impact on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	Evidence is limited on the impact of FeNO testing on health equity. If FeNO testing is used in the specialty setting only and coverage or access to specialty care is limited (e.g., by Medicaid policies), access may not be equitable. Whether FeNO testing is available to all individuals who might benefit from it depends on the coverage of this test by various health care insurance policies.	Guidelines can influence insurance coverage decisions, and the clinical policies of insurers and federal and state agencies should be based on the evidence on FeNO testing and ensure access to appropriate asthma diagnostic and monitoring services.

Abbreviations: FeNO, fractional exhaled nitric oxide.

Evidence Summary: Asthma Management Strategy That Includes Fractional Exhaled Nitric Oxide Testing vs. Usual or Standard Care That Does Not Include This Testing

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with usual or standard care without FeNO testing	Risk difference or mean difference for management strategy with FeNO testing
RATES OF DIFFERENT TYPES OF EXACERBATIONS (*CRITICAL* OUTCOMES)					
Requiring hospitalization Follow-up: 16.8 to 52 weeks	1,598 adults and children (9 RCTs)[1-9]	Low[a]	**OR: 0.70** (0.32 to 1.55)	29/788 (3.7%)	**Favors intervention** 20/810 (2.5%) 11 fewer per 1,000 (from 25 fewer to 19 more)
Requiring systemic corticosteroids Follow-up: 16.8 to 70 weeks	1,664 adults and children (10 RCTs)[1-3,5,7-12]	Moderate[a]	**OR: 0.67** (0.51 to 0.90)	205/828 (24.8%)	**Favors intervention** 156/836 (18.7%) 67 fewer per 1,000 (from 104 fewer to 19 fewer)
Number of individuals with asthma (adults) with at least one event Follow-up: 17 to 70 weeks	1,536 adults (6 RCTs)[5-8,12,13]	High	**OR: 0.62** (0.45 to 0.86)	170/769 (22.1)	**Favors intervention** 132/767 (17.2%) 111 fewer per 1,000
Number of individuals with asthma (children) with at least one event Follow-up: 17 to 70 weeks	733 children(7 RCTs)[1-4,9-11]	High	**OR: 0.50** (0.31 to 0.82)	Not available[b]	**Favors intervention** 116 fewer per 1,000
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
ACT (MID: ≥3.0) Follow-up: 17 to 70 weeks	1,431 adults and children (6 RCTs)[5-9,14]	Low[c]		**No difference** MD: –0.07 (from 0.21 lower to 0.05 higher)	

Evidence Summary: Asthma Management Strategy That Includes Fractional Exhaled Nitric Oxide Testing vs. Usual or Standard Care That Does Not Include This Testing

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with usual or standard care without FeNO testing	Risk difference or mean difference for management strategy with FeNO testing
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ (MID: ≥0.5) Follow-up: 28 to 52 weeks	621 adults (2 RCTs)[13,14]	Low[a]		MD: 0.00 (from 0.64 lower to 0.64 higher)	
PACQLQ (MID: ≥0.5) Follow-up: 28 to 52 weeks	380 children (3 RCTs)[1,3,9]	Low[a]		MD: 0.00 (from 0.64 lower to 0.64 higher) MD: 0.09 (from 0.28 lower to 0.47 higher)	

Abbreviations: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FeNO, fractional exhaled nitric oxide; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; MID, minimally important difference; OR, odds ratio; PACQLQ, Pediatric Asthma Caregiver's Quality of Life Questionnaire; RCT, randomized controlled trial.

Footnotes, including GRADE explanations

a. The Expert Panel rated this outcome down for imprecision because the confidence interval crosses the threshold of clinical significance or because the boundaries of the confidence interval included benefit and harm.

b. The Agency for Healthcare Research and Quality (AHRQ) systematic review report did not provide the data for the event rates for exacerbations from the seven RCTs in children.

c. The AHRQ systematic review report rated this outcome down for imprecision.[15]

Harms: There were no reported direct harms from FeNO testing.

New evidence

Yes. [16]

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Evidence to Decision Table III — Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Measurement in Predicting Future Development of Asthma in Individuals Ages 5 Years and Older

Background

This table addresses the diagnostic accuracy of FeNO measurement in predicting the future development of asthma in children ages 0–4 years. The table addresses Key Question 1e in the systematic review and Question 2.5 in Section II of this report: 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?
The Expert Panel defines "recurrent wheezing" as clinically significant periods of bronchial or respiratory tract wheezing that is reversible or fits the clinical picture of bronchospasm on the basis of clinical history and a physical examination. The Expert Panel considered prediction probabilities of less than 60% to be not clinically useful.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Don't know	The certainty of evidence is very low that a high FeNO level is associated with a future diagnosis of asthma. Evidence is limited to show that such a prediction leads to better outcomes that are important to individuals with asthma.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Moderate	The FeNO test has no reported direct harms. The Expert Panel was concerned, however, that being labeled as having asthma may lead to undesirable effects, including labeling bias; exclusion from sports or other activities; and a lower threshold for treatments, such as inhaled corticosteroids (which may be harmful in children).	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Very low	Nine studies addressed the ability of FeNO measures in children younger than 5 years to predict the subsequent development of asthma after age 5 years. All of these studies were correlational; six were nonrandomized longitudinal studies, and three were cross-sectional studies. Only three studies specifically examined the ability of FeNO testing to predict a future diagnosis of asthma; the remaining studies assessed the ability of FeNO testing to predict future wheezing or a positive Asthma Predictive Index score.	

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Possibly important uncertainty or variability	No research has assessed how different individuals with asthma and their families value different outcomes. In the Expert Panel's judgment, these values might vary greatly, and some individuals with asthma may value quality of life or asthma control more than exacerbations. Therefore, different individuals with asthma are likely to make different choices about the intervention. Also, the burden of FeNO testing could vary because of differences in costs and access for different individuals with asthma. Different parents might also feel differently about knowing that their child is or is not likely to develop asthma in the future.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know	The evidence does not favor the intervention because its undesirable effects outweigh its desirable effects. However, no comparison intervention has been studied.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	Little research has been conducted on the acceptability of FeNO testing to predict a future asthma diagnosis, and especially on the acceptability of testing in children ages 0–4.	Given the overall safety of the test, FeNO measurement is likely to be acceptable to some parents if it is sufficiently accurate and its findings are sufficiently actionable.

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Few, if any studies, of FeNO testing have been conducted in primary care settings. The costs of FeNO equipment and FeNO tests may limit the test's use.	The current use of FeNO measurement in many specialists' offices suggests that testing in these settings is feasible and already done in practice. After reviewing the costs and logistics of FeNO testing, the Expert Panel concluded that the intervention would have limited use in primary care settings, although its use might be more common in the collaborative care models of some health care systems. FeNO measurement in very young children is more likely to be feasible when offline methods are used, according to the standards of the American Thoracic Society and European Respiratory Society.[1]

Equity: What would be the impact on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	Evidence is limited on the impact of FeNO testing on health equity.	If FeNO testing is used in the specialty setting only and coverage or access to specialty care is limited (e.g., by Medicaid policies), access may not be equitable. However, whether FeNO testing is available to all individuals who might benefit from it depends on the coverage of this test by various health care insurance policies. Guidelines can influence insurance coverage decisions, and the clinical policies of insurers and federal and state agencies should be based on the evidence on FeNO testing and ensure access to appropriate asthma diagnostic and monitoring services.

Abbreviations: FeNO, fractional exhaled nitric oxide.

Evidence Summary: Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Measurement in Children Ages 0–4 years in Predicting Future Development of Asthma at Ages 5 Years and Older

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)
Diagnosis of asthma and/or wheezing	592 infants and children (3 observational studies)	Very low[a]		Study 1: In children ages 3–4 years with symptoms suggesting asthma (N = 306), FeNO test results predicted a physician diagnosis of asthma at age 7 and wheezing at 8 years (OR in models ranged from 2.0 to 3.0).[2] Study 2: Infants with a mean age of 11 months (N = 116) with eczema and a high FeNO level had a greater risk of developing asthma at age 5. For each 1 ppb, the OR was 1.13 (95% CI, 1.01 to 1.26).[3] Study 3: In children (N = 170) ages 2–4 years with recurrent wheezing, neither FeNO levels nor changes in FeNO levels after 8 weeks of ICS therapy predicted asthma diagnosis at age 6 (diagnosis was verified by two pediatric pulmonologists). The OR was 1.02 (95% CI, 0.98 to 1.05) for FeNO levels and 1.01 (95% CI, 0.99 to 1.04) for changes in FeNO levels.[4]

Abbreviations: CI, confidence interval; FeNO, fractional exhaled nitric oxide; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICS, inhaled corticosteroid; OR, odds ratio.

Footnotes, including GRADE explanations

a. The Agency for Healthcare Research and Quality systematic review report rated this outcome down for risk of bias (because of observational studies) and inconsistency.

Harms: There were no reported direct harms from FeNO testing.

New evidence

No.

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Evidence to Decision Table IV — Acaricide (with or without Other Interventions) Versus Placebo or Other Mite-Mitigation Interventions for Individuals with Asthma

Background

Many common indoor inhalant allergens have been associated with an increased risk of asthma exacerbations. These allergens include animal dander, house dust mites, mice, cockroaches, and mold. Numerous interventions have been designed to reduce exposure to allergens in environments where individuals with asthma live, work, learn, play, and sleep. These interventions include use of acaricides (house dust mite pesticides), air purification systems, carpet removal or vacuuming, specially designed mattress covers and pillowcases, mold mitigation, pest control techniques, and containment or removal of pets.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	For single-component interventions, no studies have provided data on exacerbations or asthma control; quality of life and asthma symptoms did not differ between individuals in acaricide-treated and placebo environments. For multicomponent interventions, two studies had inconclusive results on exacerbations and found no differences in asthma symptoms between the acaricide and placebo groups. These study reports did not provide data on asthma control or quality of life.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Don't know	Study reports did not provide data on harms. Theoretically, harms could be associated with acaricide because it is a chemical.	Users are likely to incur out-of-pocket expenses.

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Possibly important uncertainty or variability	Individuals with asthma might be averse to using chemicals (as well as to paying for acaricide out of pocket) for an intervention lacking clear benefits. However, some individuals with asthma might want to use the intervention.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Does not favor either the intervention or the comparison		

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	Acceptability may vary by stakeholder.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Do-it-yourself kits are available.	

Equity: What would be the impact on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know		

Evidence Summary: Single-Component Acaricide Interventions vs. Placebo for Individuals with Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
EXACERBATIONS (*CRITICAL* OUTCOME)				
Not reported				
ASTHMA CONTROL (*CRITICAL* OUTCOME)				
Not reported				
QUALITY OF LIFE (*CRITICAL* OUTCOME)				
Undefined scale Follow-up: 26 weeks	30 (1 RCT)[1]	Very low[b,c]	—	**Inconclusive** The study found no between-group difference. The study report shows data graphically and does not provide an estimation of variability (N = 17 for placebo, N = 13 for acaricide).
ASTHMA SYMPTOMS (*CRITICAL* OUTCOME)				
Parent and physician rating of asthma severity, disruption of daily activity, and frequency of wheezing[a] Undefined scale Follow-up: 26 weeks	35 (1 RCT)[2]	Very low[c,d]	—	**Inconclusive** Both parent and physician ratings of severity and disruption of daily activity improved, but the results showed no difference in frequency of wheezing (N = 18 for placebo, N = 17 for acaricide).
OTHER OUTCOMES (IMPORTANT OUTCOME)				
Health care utilization (rescue medication use)				**Not reported**

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

Footnotes, including GRADE explanations

a. The Expert Panel reviewed the studies that measured asthma symptoms using various nonvalidated symptom scales. One study showed no differences between the acaricide and control groups in both parent and physician ratings of asthma severity and disruption of daily activity, or in the frequency of wheezing.

b. The Agency for Healthcare Research and Quality systematic review report rated this outcome down for risk of bias because the study by Bahir (1997) had a high attrition rate and unclear sequence generation/allocation concealment.

c. The Expert Panel rated this outcome down twice for imprecision, in part because of very small samples.

d. The Expert Panel rated this outcome down for risk of bias because the Geller-Bernstein (1995) study had a high attrition rate and unclear sequence generation/allocation concealment.

Evidence Summary: Single-Component Acaricide Interventions Versus Placebo or Other Mite-Mitigation Interventions for Individuals with Asthma

The Agency for Healthcare Research and Quality systematic review report found no data on *important* or *critical* outcomes

Evidence Summary: Multicomponent Interventions that Include Acaricide vs. Placebo for Individuals with Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
EXACERBATIONS (*CRITICAL* OUTCOME)				
ED visits or hospitalizations Follow-up: 16 to 52 weeks	204 (2 RCTs)[3,4]	Very low[a,b]	—	**Inconclusive** One RCT[4] of 44 mixed-population participants found no difference in numbers of ED visits or hospitalizations. A second RCT[3] in 160 mixed-population participants had no between-group comparison. This study showed that the number of hospitalizations declined significantly in the intervention group.
ASTHMA CONTROL (*CRITICAL* OUTCOME)				
Not reported				
QUALITY OF LIFE (*CRITICAL* OUTCOME)				
Not reported				
ASTHMA SYMPTOMS (*CRITICAL* OUTCOME)				
Frequency of symptoms[c] Follow-up: 20 to 52 weeks	306 (4 RCTs)[4-7]	High	—	**No difference** Two RCTs[6,7] in 192 adults, one RCT[4] in 44 mixed-population participants, and one RCT[5] in 70 children found no differences in frequency of symptoms.
OTHER OUTCOMES (IMPORTANT OUTCOME)				
Health care utilization (use of bronchodilator or any asthma medication) Follow-up: 24 weeks	70 (1 RCT)[5]	Low[b]	—	**Inconclusive** One RCT in 70 children showed significantly less use of bronchodilators or any asthma medication.

Abbreviations: CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

Footnotes, including GRADE explanations

a. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for inconsistency.

b. The AHRQ systematic review report noted substantial imprecision in the evidence for this outcome.

c. The Expert Panel reviewed studies with data on asthma symptoms that were measured using various nonvalidated symptom scales. Two studies with data on asthma symptom frequency showed no differences between groups.

Harms: No adverse events were reported.

New evidence

No.

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