

## Cystic Fibrosis Foundation Pulmonary Guidelines

### Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis

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#### Abstract

**Rationale:** Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulators are a new class of medications targeting the underlying defect in CF. Ivacaftor (IVA) and IVA combined with lumacaftor (LUM; IVA/LUM) have been approved by the U.S. Food and Drug Administration (FDA) for use in patients with CF. However, the FDA label for these medications encompasses patient groups that were not studied as part of the drug approval process. CF clinicians, patients, and their families have recognized a need for recommendations to guide the use of these medications.

**Objective:** Develop evidence-based guidelines for CFTR modulator therapy in patients with CF.

**Methods:** A multidisciplinary committee of CF caregivers and patient representatives was assembled. A methodologist, an epidemiologist, a medical librarian, and a biostatistician were recruited to assist with the literature search, evidence grading, and generation of recommendations. The committee developed clinical questions using the Patient-Intervention-Comparison-Outcome format. A systematic review was conducted to find relevant publications. The evidence was then evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach, and recommendations were made based on this analysis.

**Results:** For adults and children aged 6 years and older with CF due to gating mutations other than G551D or R117H, the guideline panel made a conditional recommendation for treatment with IVA. For those with the R117H mutation, the guideline panel made a conditional recommendation for treatment with IVA for 1) adults aged 18 years or older, and 2) children aged 6–17 years with a forced expiratory volume in 1 second (FEV<sub>1</sub>) less than 90% predicted. For those with the R117H mutation, the guideline panel made a conditional recommendation against treatment with IVA for 1) children aged 12–17 years with an FEV<sub>1</sub> greater than 90% predicted, and 2) children less than 6 years of age. Among those with two copies of F508del, the guideline panel made a strong recommendation for treatment with IVA/LUM for adults and children aged 12 years and older with an FEV<sub>1</sub> less than 90% predicted; and made a conditional recommendation for treatment with IVA/LUM for 1) adults and children aged 12 years or older with an FEV<sub>1</sub> greater than 90% predicted, and 2) children aged 6–11 years.

**Conclusions:** Using the GRADE approach, we have made recommendations for the use of CFTR modulators in patients with CF. These recommendations will be of help to CF clinicians, patients, and their families in guiding decisions regarding use of these medications.

**Keywords:** ivacaftor; Clinical Practice Guidelines; Grading of Recommendations Assessment, Development, and Evaluation; lumacaftor

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Cystic fibrosis (CF) is an autosomal recessive disease that is caused by mutations in the gene encoding the CF transmembrane conductance regulator protein (CFTR) (1). Since the original description of CF in the 1930s (2, 3), treatment of this disease has focused on end organ effects, primarily pancreatic enzyme replacement therapy for pancreatic insufficiency, and antibiotics, airway clearance, and mucolytics to treat lung disease (4). However, in the last several years, CFTR modulators, small molecules that can partially restore function in mutated CFTR, have been developed and introduced into clinical practice (5).

The first CFTR modulator approved for clinical use was ivacaftor (IVA) (6, 7). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open-channel probability in cells expressing CFTR from patients with the G551D mutation, a gating mutation that results in loss of ion conductance (8). In clinical trials, IVA therapy resulted in lower sweat chloride (a biomarker of CFTR function), improved lung function, quality of life, and nutritional indices in patients with CF with the G551D mutation (9). The U.S. Food and Drug Administration (FDA) approved IVA for patients with CF aged 12 years or older with the G551D mutation in 2012. From 2013 to 2015, approval was expanded to include patients aged 6 years or older and those with other gating mutations. Even with the expanded indication, only about 10% of patients with CF in the United States carry mutations that are responsive to IVA (10).

The most common CFTR mutation that causes CF is F508del, which results in improper protein folding, leading to its degradation in the endoplasmic reticulum and decreased ion conductance (4, 10). Approximately 50% of patients with CF are homozygous for F508del, and another 40% are compound heterozygotes, with one F508del mutation and another CF-causing mutation. Because surface expression of F508del-CFTR is minimal, IVA alone has no significant effect on CFTR function in patients carrying two copies of this mutation. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein (11, 12). LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to have a clinical impact on CF lung disease. However, the combination

of LUM, which increases CFTR expression at the cell surface, and IVA, which increases conductance in the increased surface CFTR, can increase CFTR function to a level that can potentially affect clinically meaningful outcomes (11). Clinical trials of combination IVA/LUM therapy in patients with CF homozygous for F508del demonstrated improved lung function and reduced pulmonary exacerbations (13). In 2015, IVA/LUM was approved by the FDA for patients with CF aged 12 years or older and homozygous for F508del. In 2016, FDA labeling was expanded to include patients aged 6 years or older.

The introduction of CFTR modulators has revolutionized CF care and ushered in the possibility of preventing disease progression by correcting the fundamental defect in CF. However, questions remain regarding how to apply these therapies in clinical practice. Both IVA and LUM are oral medications that can result in systemic side effects and drug interactions (14). CFTR modulator therapy can improve pulmonary abnormalities due to CF, such as ventilation heterogeneity, but these abnormalities return upon cessation of therapy (15), indicating that CFTR modulator therapy is a chronic, lifelong treatment. Balancing the potential benefits of these medications against these risks is not addressed in the prescribing information that is distributed with every FDA-approved medication.

Randomized clinical trials (RCTs) used for FDA approval enroll a narrowly defined subset of patients and are designed to optimize detection of a therapeutic effect (16, 17). Although FDA approval for these medications extends to patient populations that were not studied as part of the pivotal phase 3 preapproval clinical trials (e.g., patients with severe lung disease or children with very mild lung disease), evidence-based recommendations for CFTR modulator therapy in these populations are not available. This has affected the access of patients with CF to these medications (J. Erdo, personal communication, Cystic Fibrosis Foundation) (16–20). Given the high costs of these medications (21), patients, families, and clinicians are in need of guidance based on a thorough and rigorous review of the data.

With the above background in mind, the Cystic Fibrosis Foundation (CFF) sponsored the creation of a guideline development committee consisting of

independent CF caregivers from multiple disciplines, as well as patient representatives. The objective of the committee was to develop guidelines to help inform discussions with patients and families and decision making by CF professionals. To achieve this objective, we conducted a systematic review of the literature on CFTR modulators and developed evidence-based recommendations for their use in specific populations of patients with CF.

## Use of This Guideline

This guideline is not meant to establish a standard of care. Rather, it represents an effort to summarize evidence and provide sensible clinical recommendations based on that evidence. Clinicians, patients, third-party payers, other stakeholders, and the courts should never view these recommendations as dictates. No guideline or specific recommendations can take into account all of the unique clinical circumstances leading to therapy decisions for individual patients. Therefore, no one charged with evaluating clinicians' actions should attempt to rigidly apply the recommendations from this guideline in a global fashion. This guideline is not intended to be a comprehensive review of the treatment of CF, but rather to provide evidence-based recommendations for use of CFTR modulators in different populations of patients with CF. Clinicians, patients with CF, and parents of patients with CF will be able to use these recommendations when considering CFTR modulator therapy.

## Methods

### Definitions

For this guideline, the committee defined patients with CF as individuals who met CFF criteria for diagnosis of CF (i.e., a clinical presentation consistent with CF, a positive CF newborn screening test, or family history of CF) combined with evidence of abnormal CFTR function, as demonstrated by elevated sweat chloride, detection of two CF-causing CFTR mutations, or abnormal nasal potential differences (22). CFTR modulators are drugs that have been shown to partially restore CFTR function through either *in vitro* or *in vivo* assays (7). Only clinically

available CFTR modulators that have been approved for use by the FDA were considered in this review.

**Process**

Co-chairs (E.T.N. and C.L.R.) of the committee were selected by the CFF based on their experience in guideline development and their membership on the CFF Guidelines Committee. The committee for these guidelines was composed of an independent, multidisciplinary group of individuals with expertise and experience in CF care, and included pediatric pulmonologists, adult pulmonologists, a pharmacist, a nurse practitioner, and a respiratory therapist. An adult CF patient and a parent of a child with CF were included in the committee. To assist with the systematic data review and evidence grading, the committee also recruited a medical librarian, methodologist, clinical epidemiologist, and biostatistician.

When choosing committee members for these guidelines, all potential committee members were asked to complete a conflict of interest (COI) questionnaire regarding both fiduciary and financial relationships with pharmaceutical companies involved in the production of clinically available CFTR modulators. The COI questionnaires were examined by a neutral and unbiased member of the CFF Guidelines Steering Committee as well as the CFF Director of Medical Compliance. Any potential committee member who disclosed such a relationship was not invited to participate on the committee, and several members of the CFF Guidelines Committee were excluded because of potential conflicts of interest.

Due to the CFF’s potential COI in the creation of these guidelines, no CFF staff member participated in writing or discussion of the recommendations, and the CFF neither endorsed nor declined to endorse these recommendations. The only CFF staff present for the discussion of these recommendations were the Practice Guidelines Specialist and the Director of Medical Compliance, and neither of them participated in the creation of questions or the development of any recommendations. The CFF’s role in the development of these guidelines was limited to funding for face-to-face meetings, telephone conference calls, the methodologist, the biostatistician, and the clinical epidemiologist. The medical librarian was recruited from Indiana University, which did not charge any fees for her effort.

The committee used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the evidence and develop recommendations (23). GRADE classifies recommendations as strong or conditional (i.e., weak) (Table 1). The strength of the recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resources. It is important to note that a conditional recommendation means that although the majority of patients and clinicians will follow the recommendation, there will be some conditions in which the recommendation may not be appropriate given individual circumstances, and the ultimate therapeutic decision will be based on clinical factors specific and unique to

that individual patient. Conversely, even a strong recommendation should not be rigidly obeyed, and there may be circumstances under which a clinician or patient would not follow a strong recommendation. Further details on how we applied GRADE and the evidence-to-decision tables used to generate recommendations are available in the online supplement.

The committee developed clinical questions using the PICO (Patient, Intervention, Comparator, and Outcomes) format. In developing questions, the committee focused on issues of interest and importance to CF clinicians, patients, and their families. The committee chose not to address clinical situations for which recommendations have already been published (e.g., IVA therapy for patients aged 12 years or older with CF who carry at least one copy of the G551D mutation or 2- to 5-year-old patients with CF with gating mutations other than G551D [24, 25]) or if the question was of low priority and unlikely to change practice (e.g., IVA/LUM therapy for patients with CF with only one copy of F508del). A systematic review of peer-reviewed literature published from database inception through April 2016 was conducted in Ovid, EMBASE, PubMed, Cochrane Library Scopus, and Google Scholar. We repeated the search in September 2017 and found no relevant new citations. RCTs reflecting the PICO criteria published in English were eligible for inclusion in the meta-analysis. Full details of the data review, grading, and evidence-to-decision tables are available in the online supplement.

**Table 1.** Interpretation of the strength of grading of recommendations, assessment, development, and evaluation recommendations

Implications	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Adapted from Reference 23.

**Question 1: Should IVA versus No CFTR Modulator Treatment Be Used for Individuals with a CF Diagnosis due to Gating Mutations Other Than G551D or R117H (i.e., G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D)?**

**Background**

IVA was initially approved for individuals with CF with the G551D genotype, a class III gating mutation and present in about 3.5% of the U.S. CF population. A number of less common class III mutations share the same gating defect as G551D and would be expected to have a similar response to IVA therapy (26, 27). The FDA approved the use of IVA for individuals aged 6 years or older with these mutations in February 2014, and extended this indication to individuals aged 2 years or older in March 2015.

**Summary of the Evidence**

Our search identified one randomized, placebo-controlled cross-over study comparing the effectiveness of IVA versus placebo for the treatment of patients with CF with a copy of one of the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutation (28). A total of 39 patients aged 6 years and older with a percent predicted forced expiratory volume in 1 second (PPFEV<sub>1</sub>) of 40% or greater was randomized to receive either IVA 150 mg every 12 hours or placebo for 8 weeks. After a 4-week washout period, subjects then crossed over to the alternate treatment arm, IVA or placebo, for an additional 8 weeks. The initial phase of the study was followed by a 16-week open-label phase where all patients received IVA. The absolute mean difference in PPFEV<sub>1</sub> improved among participants treated with IVA (13.76; 95% confidence interval [CI] = 13.11–14.41). Quality of life, as measured by the respiratory domain of the CF Questionnaire–Revised (CFQ-R) (29) score, increased above the minimum clinically important difference of 4.0 (12.82; 95% CI = 11.81–13.83). Nutritional status, as measured by body mass index (BMI), also improved in subjects treated with IVA with a mean difference of 0.66 kg/m<sup>2</sup> (95% CI = 0.44–0.88). The relative risk of exacerbations in patients receiving IVA was reduced, but not significantly (RR = 0.80; 95% CI = 0.37–1.70). The improvements in

PPFEV<sub>1</sub>, CFQ-R scores, and BMI were seen in all treated patients, with the exception of G970R. Sweat chloride concentrations also fell with treatment in all genotypes, again with the exception of G970R. The G970R mutation results in aberrant splicing and a truncated protein that is not expressed on the cell surface, rendering it unresponsive to a CFTR potentiator (30). Fewer serious adverse events leading to treatment discontinuation occurred among patients receiving IVA; however, the estimate was not statistically significant (RR = 0.56; 95% CI = 0.18–1.74).

**Recommendations**

Table 2 summarizes our recommendations for question 1 stratified by age and PPFEV<sub>1</sub>, and comments for each recommendation are listed below. Details of the evidence grading and evidence-to-decision tables for each recommendation are available in the online supplement.

**Recommendation 1.** The committee recommends IVA for individuals aged 2–5 years with a diagnosis of CF and gating mutations other than G551D or R117H. For individuals under 2 years of age, the committee makes no recommendation.

*Remarks: for individuals aged 2–5 years, the committee followed the recommendation of the CFF Preschool Guidelines (25). For individuals under 2 years of age, the committee makes no recommendation, because, at present there is no clinically available formulation or dosing information in this age range.*

**Recommendation 2.** The committee suggests IVA for individuals aged 6–11

years with a diagnosis of CF with PPFEV<sub>1</sub> less than 40% and a gating mutation other than G551D or R117H (conditional recommendation, very low certainty in the evidence).

*Remarks: a patient with PPFEV<sub>1</sub> less than 40% in this age group is presenting with rapid progression of disease and the threshold to use therapies of potential benefit is lower. Decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 3.** The committee suggests IVA treatment for individuals aged 6–11 years with a diagnosis of CF with PPFEV<sub>1</sub> 40%–90% and a gating mutation other than G551D or R117H (conditional recommendation, low certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 4.** The committee suggests IVA be used for individuals aged 6–11 years with a diagnosis of CF with PPFEV<sub>1</sub> greater than 90% and a gating mutation other than G551D or R117H (conditional recommendation, very low certainty in the evidence).

*Remarks: even though the expected absolute change might be small, patients might be more likely to maintain FEV<sub>1</sub> predicted. Decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 5.** The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with PPFEV<sub>1</sub> less than 40% and a gating mutation other

**Table 2.** Summary of recommendations for patient, intervention, comparator, and outcomes question 1 (ivacaftor for patients with cystic fibrosis due to gating mutations other than G551D or R117H)

Subgroup No.	Age (Yr)	PPFEV <sub>1</sub> (%)	Certainty	Recommendation
1	2–5	N/A	N/A	Recommend for 2–5 yr* No recommendation for <2 yr
2	6–11	<40	Very low	Conditional for
3	6–11	40–90	Low	Conditional for
4	6–11	>90	Low	Conditional for
5	12–17	<40	Low	Conditional for
6	12–17	40–90	Moderate	Conditional for
7	12–17	>90	Moderate	Conditional for
8	18+	<40	Low	Conditional for
9	18+	40–90	Moderate	Conditional for
10	18+	>90	Moderate	Conditional for

*Definition of abbreviations:* N/A = not applicable; PPFEV<sub>1</sub> = percent predicted forced expiratory volume in 1 second.

\*Based on the Cystic Fibrosis Preschool Guidelines recommendations (25).



than G551D or R117H (conditional recommendation, low certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 6.** The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with PPFEV<sub>1</sub> 40%–90% and a gating mutation other than G551D or R117H (conditional recommendation, moderate certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 7.** The committee suggests IVA for individuals aged 12–17 years with a diagnosis of CF with PPFEV<sub>1</sub> greater than 90% and a gating mutation other than G551D or R117H (conditional recommendation, moderate certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 8.** The committee suggests IVA for individuals aged 18 years or older with a diagnosis of CF with PPFEV<sub>1</sub> less than 40% and a gating mutation other than G551D or R117H (Conditional recommendation, Low certainty in the evidence).

*Remarks: Decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 9.** The committee suggests IVA for individuals with a diagnosis of CF aged 18 years or older with PPFEV<sub>1</sub> 40%–90% and a gating mutation G551D or R117H (conditional recommendation, moderate certainty in the evidence).

*Remarks: Decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

**Recommendation 10.** The committee suggests IVA for individuals aged 18 years or older with a diagnosis of CF with PPFEV<sub>1</sub> greater than 90% and a gating mutation G551D or R117H (conditional recommendation, moderate certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient.*

### Justification and Implementation Considerations

These recommendations place a high value on the potential improvement of patient-important outcomes, such as quality

of life and pulmonary exacerbations, and objective measures linked to mortality, such as PPFEV<sub>1</sub>, and less value on the substantial expected costs of the therapy. The balance between these values will vary among patients with these gating mutations. As the number of individuals with any single mutation was very small, comparisons between differing gating mutations could not be made. Although patients with PPFEV<sub>1</sub> less than 40% were not included in the one RCT identified, a recommendation was made with a lower degree of certainty due to indirectness. There was no upper limit cutoff for PPFEV<sub>1</sub>. The available analysis did not stratify by age or PPFEV<sub>1</sub> status.

The committee agreed that patients, parents, and physicians would be likely to use this medication in most individuals. The high cost of the medication may limit the acceptability of this therapy to some key stakeholders, especially payers and capitated closed health systems. The justification for the recommendations for individual subgroups for this PICO question can be found in the online supplement.

### Question 2: Should IVA versus No CFTR Modulator Treatment Be Used for Individuals with a CF Diagnosis Due to the R117H Mutation?

#### Background

The R117H mutation causes both impaired CFTR channel conductance as well as reduced gating, and is present in approximately 2.8% of individuals with CF in the U.S. CFF Patient Registry (10). R117H is associated with varying clinical consequences and is influenced by the poly T status of the *cis*-located intron 8 polythymidine tract (31, 32). The presence of 5 thymidines (5T) results in reduced splicing efficiency and reduced CFTR messenger RNA, which can reduce the ion conductance in R117H mutant CFTR. The FDA approved the use of IVA for individuals aged 6 years and older with this mutation in December 2014 and extended this indication to individuals 2 years and older in March 2015.

#### Summary of the Evidence

Our search identified one RCT comparing the efficacy of IVA versus placebo in patients with CF with at least one copy of the R117H mutation (33). A total of 69 study subjects aged 6 years or older and with a

PPFEV<sub>1</sub> of 40% or greater were randomized to receive either IVA 150 mg every 12 hours or placebo for 24 weeks. Randomization was stratified by age groups (6–11, 12–17, and ≥18 yr) and PPFEV<sub>1</sub> (<70%, 70%–90%, and >90%). For the entire population, the absolute mean difference in PPFEV<sub>1</sub> between IVA and placebo was 2.10 (95% CI = 1.56–2.64). The mean difference in the CFQ-R respiratory domain was 8.40 (95% CI = 7.36–9.44). Prespecified subgroup analysis demonstrated an improvement in the mean difference of PPFEV<sub>1</sub> in individuals aged 18 years or older versus placebo (5.00; 95% CI = 4.25–5.75), but not individuals aged 6–11 years (–6.30; 95% CI = –8.07 to –4.53). Insufficient numbers of patients aged 12–17 years precluded a separate subgroup analysis. Overall, the prevalence of 5T and 7T in the IVA group was 62% and 35%, respectively, whereas, in the placebo group, it was 77% and 20%, respectively. Similar results were seen in both 5T and 7T study subjects.

#### Recommendations

Table 3 summarizes our recommendations for question 2 stratified by age and PPFEV<sub>1</sub>, and remarks for each recommendation are listed below. Details of the evidence grading and evidence-to-decision tables for each recommendation are available in the online supplement.

**Recommendation 11.** The committee suggests against IVA therapy for individuals aged 0–5 years and with a CF diagnosis due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: this recommendation placed high value on the substantial expected costs of therapy and potential side effects against lack of potential for improvement in patient-important outcomes, such as lung function in age range that cannot be easily stratified by lung function. The data considered for this recommendation were comprised of individuals aged 6–11 years, which contained few individuals with compromised lung function and with possible overrepresentation of individuals with limited disease penetrance. Parents and providers may be more likely to use this medication in situations where more severe or more rapidly progressive disease, assessed by other criteria, is present.*

**Recommendation 12.** The committee suggests IVA for individuals aged 6–11

**Table 3.** Summary of recommendations for patient, intervention, comparator, and outcomes question 2 (ivacaftor for patients with cystic fibrosis with the R117H mutation)

Subgroup No.	Age (Yr)	PPFEV <sub>1</sub> (%)	Certainty	Recommendation
11	0–5	N/A	Very low	Conditional against
12	6–11	<40	Very low	Conditional for
13	6–11	40–90	Very low	Conditional for
14	6–11	>90	Low	Conditional against
15	12–17	<40	Very low	Conditional for
16	12–17	40–90	Very low	Conditional for
17	12–17	>90	Very low	Conditional against
18	18+	<40	Very low	Conditional for
19	18+	40–90	Moderate	Conditional for
20	18+	>90	Low	Conditional for

Definition of abbreviations: N/A = not applicable; PPFEV<sub>1</sub> = percent predicted forced expiratory volume in 1 second.

years with PPFEV<sub>1</sub> less than 40% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: the overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in situations where more severe or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while being adherent to usual care.*

**Recommendation 13.** The committee suggests IVA treatment for individuals aged 6–11 years with PPFEV<sub>1</sub> 40%–90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: as previously here, patients, parents, and providers would be more likely to use this medication in situations where younger patients are already demonstrating reduced lung function.*

**Recommendation 14.** The committee suggests that IVA not be used for individuals aged 6–11 years with PPFEV<sub>1</sub> greater than 90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, low certainty in the evidence).

*Remarks: the panel believed that this group most closely matched the data from Moss and colleagues (33), which demonstrated a fall in PPFEV<sub>1</sub>, and patients, parents, and providers would be less likely to use this medication in individuals with possibly limited disease penetrance.*

**Recommendation 15.** The committee suggests IVA for individuals aged 12–17 years with PPFEV<sub>1</sub> less than 40% with a

diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: patients, parents, and providers would be more likely to use this medication in situations where younger patients are already demonstrating reduced lung function.*

**Recommendation 16.** The committee suggests IVA for individuals aged 12–17 years with PPFEV<sub>1</sub> 40%–90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: as previously here, patients, parents, and providers would be more likely to use this medication in situations where younger patients are already demonstrating reduced lung function.*

**Recommendation 17.** The committee suggests against IVA for individuals aged 12–17 years with PPFEV<sub>1</sub> greater than 90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, moderate certainty in the evidence).

*Remarks: although data were limited for this age range, the panel believed this group most closely matched the data for the 6- to 11-year group, which demonstrated a fall in PPFEV<sub>1</sub> with IVA therapy. Patients, parents, and providers would again be less likely to use this medication in individuals with possibly limited disease penetrance.*

**Recommendation 18.** The committee suggests IVA for individuals aged 18 years or older with PPFEV<sub>1</sub> less than 40% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

*Remarks: the overall consensus of the group was that patients and providers would*

*be more likely to use this medication in situations where more severe or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while being adherent to usual care.*

**Recommendation 19.** The committee suggests IVA for individuals aged 18 years or older with PPFEV<sub>1</sub> 40%–90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, moderate certainty in the evidence).

*Remarks: as previously here, patients and providers would be more likely to use this medication in situations where more severe or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while being adherent to usual care.*

**Recommendation 20.** The committee suggests IVA for individuals aged 18 years or older with PPFEV<sub>1</sub> greater than 90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, moderate certainty in the evidence).

*Remarks: although this group is likely to include individuals with low penetrance of disease, subjects in this age range demonstrated benefit with IVA therapy. Decisions on whether or not to prescribe IVA may vary based on insurance coverage and cost to the patient*

**Justification and Implementation Considerations**

This recommendation places a high value on the potential improvement of patient-important outcomes, such as lung function measured by PPFEV<sub>1</sub> and quality of life, and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H as the penetrance of this mutation is highly variable, with some individuals having minimal symptoms and others having severe disease. This variability of disease burden created difficulty in evaluating the evidence across subgroups based on age and PPFEV<sub>1</sub>. The data available did stratify by age and PPFEV<sub>1</sub> status, but representation in each stratum varied widely. The younger patient cohort included very few individuals with low lung function and was overrepresented by individuals with normal lung function, reducing the likelihood of substantial improvement from baseline. The age group 18 years or older had substantially more individuals with more severe airflow

impairment, and this group experienced more substantial improvement in PPFEV<sub>1</sub>, BMI, and CFQ-R respiratory domain scores.

The overall consensus of the committee was that patients and providers would be more likely to use this medication in situations where more moderate to severe or more rapidly progressive disease is present. Committee members felt that providers and patients would be less willing to use this therapy in patients whose lung function is normal, especially in younger age groups where no clear benefit was noted in the subanalysis, hence the conditional recommendation against IVA use for these subgroups. The justification for the recommendations for individual subgroups for this PICO question can be found on the online supplement.

### Question 3: Should IVA/LUM Combination Drug versus No CFTR Modulator Treatment Be Used in Individuals with Two Copies of the F508del Mutation?

#### Background

F508del is the most common CFTR mutation; approximately 50% of patients worldwide are homozygous and 40% are heterozygous (10). This mutation results in markedly decreased amounts of CFTR at the apical surface of respiratory epithelial cells due to its destruction in the endoplasmic reticulum (34). The small amount of protein at the cell surface demonstrates minimal gating activity. Hence, CFTR modulator therapy directed at the F508del mutation must include both a corrector to increase surface protein expression and a potentiator to augment ion conductance. LUM partially corrects CFTR misfolding, allowing increased CFTR surface expression, whereas IVA improves its gating function (8, 11).

#### Summary of the Evidence

Our search identified four papers in which IVA/LUM was used to treat patients with CF homozygous for F508del: three reported results from three placebo-controlled RCTs (13, 35, 36), and one was an open-label extension study (37). Wainwright and colleagues (13) and Elborn and colleagues (36) reported results from the same two RCTs. However, Elborn and colleagues stratified analysis by PPFEV<sub>1</sub>, which complemented the results reported by Wainwright and colleagues; Boyle and colleagues (35) included a cohort of

patients heterozygous for F508del, but only cohorts comprised of homozygous patients were included in their analysis. When pooled, the RCTs included 1,268 patients aged 12 years or older and with PPFEV<sub>1</sub> greater than 40%. Specific patient populations, medication doses, and duration of therapy varied among studies and among cohorts. The absolute mean difference in PPFEV<sub>1</sub> improved for patients aged 12–17 years with baseline PPFEV<sub>1</sub> 40%–90% (3.06; 95% CI = 2.40–3.72) and for patients aged 18 years or older and PPFEV<sub>1</sub> less than 40%, 40%–90%, and greater than 90% (3.51; 95% CI = 3.01–4.01; 3.92; 95% CI = 3.3 to –4.52; and 5.59; 95% CI = 3.24–7.94; respectively). Lower respiratory events decreased in both the aged 12–17 years and aged 18 years or older groups with PPFEV<sub>1</sub> 40%–90% (RR = 0.89; 95% CI = 0.80–0.99; and RR = 0.90; 95% CI = 0.82–0.98). Pulmonary exacerbation risk decreased (RR = 0.76; 95% CI = 0.66–0.88 and RR = 0.76; 95% CI = 0.66–0.88), and the CFQ-R respiratory domain score improved (mean difference [MD] = 2.61; 95% CI = 1.63–3.59; and MD = 7.33; 95% CI = 5.95–8.71) in these same groups. CFQ-R respiratory domain score also improved for patients aged 18 years or older with PPFEV<sub>1</sub> greater than 90% (16.21; 95% CI = 13.05–19.38). BMI improved in patients aged ≥ 12 years with PPFEV<sub>1</sub> of 40% or less (MD = 0.46; 95% CI = 0.38–0.53) and 40%–90% (MD = 0.27; 95% CI = 0.13–0.40). Serious adverse events decreased among patients aged 12–17 years and 18 years or older with PPFEV<sub>1</sub> 40%–90% (RR = 0.70; 95% CI = 0.66–0.88; and RR = 0.69; 95% CI = 0.56–0.85).

#### Recommendations

Table 4 summarizes our recommendations for question 3 stratified by age and PPFEV<sub>1</sub>, and remarks for each recommendation are listed below. Details of the evidence grading and evidence-to-decision tables for each recommendation are available in the online supplement.

**Recommendation 21.** The committee makes no recommendation for or against IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 0–5 years.

*Remarks: the committee chose not to make a recommendation for or against IVA/LUM combination therapy for this age*

*group, because there is no formulation of this drug that is clinically available.*

**Recommendation 22.** The committee suggests IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 6–11 years with PPFEV<sub>1</sub> less than 40%. (conditional recommendation, very low certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is balancing the potential benefits for this population versus well-documented intolerance of IVA/LUM in patients with poor lung function. Additional considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.*

**Recommendation 23.** The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> 40%–90% (conditional recommendation, very low certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. These considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.*

**Recommendation 24.** The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> greater than 90% (conditional recommendation, very low certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is whether or not patients with normal lung function will benefit from treatment through prevention of deterioration rather than improvement in PPFEV<sub>1</sub>. Other considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.*

**Recommendation 25.** The committee suggests IVA/LUM combination therapy for individuals aged 12–17 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> less than 40% (strong recommendation, moderate certainty in the evidence).

*Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is balancing the potential benefits for this population versus well-documented intolerance of IVA/LUM in patients with poor lung function.*



**Table 4.** Summary of recommendations for patient, intervention, comparator, and outcomes question 3 (ivacaftor/lumacaftor for patients with cystic fibrosis with two copies of F508del)

Subgroup No.	Age (Yr)	PPFEV <sub>1</sub> (%)	Certainty	Recommendation
21	0–5	N/A	N/A	No recommendation
22	6–11	<40	Very low	Conditional for
23	6–11	40–90	Very low	Conditional for
24	6–11	>90	Very low	Conditional for
25	12–17	<40	Moderate	Strong for
26	12–17	40–90	Moderate	Strong for
27	12–17	>90	Low	Conditional for
28	18+	<40	Moderate	Strong for
29	18+	40–90	Moderate	Strong for
30	18+	>90	Low	Conditional for

Definition of abbreviations: N/A = not applicable; PPFEV<sub>1</sub> = percent predicted forced expiratory volume in 1 second.

Additional considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

**Recommendation 26.** The committee suggests IVA/LUM combination therapy for individuals aged 12–17 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> 40%–90% (strong recommendation, moderate certainty in the evidence).

Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. These considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

**Recommendation 27.** The committee suggests IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 12–17 years with PPFEV<sub>1</sub> greater than 90%. (Conditional recommendation, Low certainty in the evidence).

Remarks: Decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is whether or not patients with normal lung function will benefit from treatment through prevention of deterioration rather than improvement in PPFEV<sub>1</sub>. Other considerations include possible drug–drug interactions, insurance coverage and cost to the patient.

**Recommendation 28.** The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> less than 40% (strong recommendation, moderate certainty in the evidence).

Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is balancing the

potential benefits for this population versus well-documented intolerance of IVA/LUM in patients with poor lung function.

Additional considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

**Recommendation 29.** The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> 40%–90% (strong recommendation, moderate certainty in the evidence).

Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. These considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

**Recommendation 30.** The committee suggests IVA/LUM combination therapy for individuals aged 18 years or older with a diagnosis of CF and two copies of the F508del mutation with PPFEV<sub>1</sub> greater than 90% (conditional recommendation, low certainty in the evidence).

Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is whether or not patients with normal lung function will benefit from treatment through prevention of deterioration rather than improvement in PPFEV<sub>1</sub>. Other considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

**Justification and Implementation Considerations**

This recommendation places a high value on the potential improvement of patient-important outcomes, such as lung function, and less value on the substantial expected

costs of the therapy. The preponderance of evidence from clinical trials demonstrates significant clinical improvement in patient-important outcomes for patients aged 12 years or older with baseline PPFEV<sub>1</sub> of 90% or less treated with combination IVA/LUM. For this reason, the committee made a strong recommendation for treatment with moderate certainty in the evidence. Patients with baseline PPFEV<sub>1</sub> greater than 90% failed to demonstrate equivalent improvements, but our ability to draw conclusions was hampered by small numbers of patients in this lung function group. Nevertheless, the committee concluded that the potential for preservation of lung function and other outcomes justified a conditional recommendation in favor of treatment. None of the studies in the analysis included patients aged 12 years or younger. The open-label trial from Milla and colleagues (38) was conducted to address this lack of data. It reported that combination IVA/LUM therapy was well tolerated and led to improvements in ventilation inhomogeneity (as measured by lung clearance index), sweat chloride, nutritional status, and health-related quality of life during 24 weeks of treatment. For this reason, the committee suggests the use of IVA/LUM therapy in children aged 6–11 years regardless of baseline PPFEV<sub>1</sub>. Another consideration in the decision to prescribe IVA/LUM is the reported increased incidence of cough and chest tightness among patients of all ages with PPFEV<sub>1</sub> less than 40% (38). Patients have generally tolerated gradual reintroduction of therapy, but early worsening of symptoms should be included in treatment discussions. In addition, potential drug–drug interactions with strong CYP3A4 inducers must be considered, especially in the setting of oral contraception. Hence, clinicians would be justified in discussing relative benefits versus risks of therapy, as well as other considerations, such as cost, with patients and families for whom therapy is suggested. The justification for the recommendations for individual subgroups for this question can be found in the online supplement.

**Limitations and Future Directions**

The available evidence for formulating this guideline was limited to six published studies, two of which were analyses of the same study population and one of which was



an open-label efficacy trial. Although these clinical trials were well designed, the inclusion and exclusion criteria did not encompass the complete ranges of PPFEV<sub>1</sub> and ages specified in our PICO subgroup analyses. The small number of studies available for review also contributed to the uncertainty of the evidence. In a number of the studies, data were not stratified by age or PPFEV<sub>1</sub>, requiring the committee to assess how generalizable the available evidence would be to a specific subgroup. Within the GRADE approach, the best available evidence is considered to inform decision making, including evidence determined to be indirect to the subgroups of interest. However, the indirectness and uncertainty of the evidence affected the strength of our recommendations and led to many of our recommendations being conditional.

Study duration was another factor that affected the strength of the evidence and our ability to assess clinical outcomes of interest. CFTR modulators are drugs that are expected to be used for the lifetime of the patient. None of the studies reported outcomes beyond 2 years, and, for some of them, the treatment period was as short as 8 weeks. This prevented the committee from being able to assess long-term effects on lung function and long-term safety. Because CFTR modulators affect the fundamental defect in CF, they may also affect disease progression, which could be reflected in a lower rate of PPFEV<sub>1</sub> decline. However, because the mean rate of PPFEV<sub>1</sub> decline in patients with CF is relatively small, an RCT powered to demonstrate a significant effect of CFTR modulators on PPFEV<sub>1</sub> decline would either require very large numbers of study subjects or a long treatment period, rendering such a study

very difficult to carry out (39, 40). One recent study, not considered by the committee because it was published after our search, did demonstrate a slower rate of PPFEV<sub>1</sub> decline in individuals homozygous for F508del receiving IVA/LUM compared with a matched cohort from the CFF Patient Registry (41). However, as this was not an RCT, the quality of the data would have been considered weak, and it would not have led to a change from a conditional to a strong recommendation.

Data available for measurement of efficacy and formulation of the treatments considered in these guidelines was limited in younger age groups, especially in the 0- to 5-year age range. Young children under 6 years of age cannot reliably perform the maximal forced expiratory maneuver required for spirometry, and robust, normal reference equations are not available, so children in this age range were not included in the studies we reviewed. Although other techniques for assessing lung function in young children are available (42), they are not widely used, and have not been fully validated in CF research and clinical care. Moreover, PPFEV<sub>1</sub> in young children with CF is usually normal (10), limiting its use as an outcome measure in clinical trials with this age group. Dosing and administration are also problematic in this age group. Although there is a formulation of IVA that is available and suitable for infant administration, pharmacokinetic data are lacking that would allow clinicians to select the appropriate dose in this age range. For IVA/LUM, no FDA-approved formulation is currently available for patients under age 6 years, although an investigational formulation is currently being used in clinical trials (clinical trial

registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) [NCT02797132]).

The development and clinical use of CFTR correctors and potentiators is in its infancy. There are several new compounds under development, and progress in this area has been rapid. Indeed, in the time between development of these guidelines and their submission for publication, the FDA has approved the use of IVA for individuals with certain residual function mutations that have demonstrated *in vitro* responsiveness to IVA therapy (26), next-generation correctors have been demonstrated to improve lung function in people with CF who are compound heterozygotes for F508del and a mutation with minimal function (43), and IVA/LUM has been shown to increase PPFEV<sub>1</sub> in children aged 6–11 years with CF and homozygous for the F508del mutation (44). In the next few years, the results of clinical trials with newer compounds and directed against different CFTR mutation will become available, leading to new FDA-approved medications and indications. We anticipate that this guideline will be expanded and updated as these newer compounds and data become available. In the meantime, the recommendations we have presented here will be helpful for clinicians, patients, and their families in making current treatment decisions regarding CFTR modulators. ■

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## References

- Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med* 2005; 352:1992–2001.
- Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *Am J Dis Child* 1938;56: 344–399.
- Fanconi G, Uehlinger E, Knauer C. Das coeliakie-syndrom bei angeborener zystischer pankreasfibromatose und bronchiektasien. *Wien Med Wochenschr* 1936;86:753–756.
- Paranjape SM, Mogayzel PJ Jr. Cystic fibrosis. *Pediatr Rev* 2014;35: 194–205.
- Lopes-Pacheco M. CFTR modulators: shedding light on precision medicine for cystic fibrosis. *Front Pharmacol* 2016;7:275.
- Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax* 2016;71:454–461.
- Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med* 2013;1: 158–163.
- Van Goor F, Hadida S, Grootenhuys PDJ, Burton B, Cao D, Neuberger T, et al. Rescue of CF airway epithelial cell function *in vitro* by a CFTR potentiator, VX-770. *Proc Natl Acad Sci USA* 2009;106: 18825–18830.
- Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al.; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365: 1663–1672.
- Cystic Fibrosis Foundation patient registry 2015: annual data report. Bethesda: Cystic Fibrosis Foundation; 2016.
- Van Goor F, Hadida S, Grootenhuys PDJ, Burton B, Stack JH, Straley KS, et al. Correction of the F508del-CFTR protein processing defect *in vitro* by the investigational drug VX-809. *Proc Natl Acad Sci USA* 2011;108:18843–18848.

- 12 Van Goor F, Straley KS, Cao D, González J, Hadida S, Hazlewood A, *et al.* Rescue of DeltaF508-CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. *Am J Physiol Lung Cell Mol Physiol* 2006;290:L1117–L1130.
- 13 Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, *et al.*; TRAFFIC Study Group; TRANSPORT Study Group. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:220–231.
- 14 Pettit RS, Fellner C. CFTR modulators for the treatment of cystic fibrosis. *P&T* 2014;39:500–511.
- 15 Altes TA, Johnson M, Fidler M, Botfield M, Tustison NJ, Leiva-Salinas C, *et al.* Use of hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with cystic fibrosis. *J Cyst Fibros* 2017;16:267–274.
- 16 O'Sullivan BP. Importance of off-label options for treating serious lung diseases. *Ann Am Thorac Soc* 2016;13:1879–1880.
- 17 VanDevanter DR, Heltshe SL, LiPuma JJ. Potential for therapeutic benefit among cystic fibrosis populations excluded from clinical trials or labeling of marketed therapies. *Ann Am Thorac Soc* 2016;13:1890–1893.
- 18 Division of Medical Assistance Programs OHA. Oregon Medicaid Pharmaceutical Services prior authorization criteria: Medicaid PA Criteria, 2015 July 30 [updated 2016 Jan 1; accessed 2018 Jan 25]. Available from: <https://www.oregon.gov/oha/healthplan/tools/oregon>.
- 19 Illinois Department of Healthcare and Family Services. Orkambi (lumacaftor-ivacaftor tablet): prior authorization criteria. 2015 Sep [accessed 2017 Sep 1]. Available from: <http://www.illinois.gov/hfs/sitecollectiondocuments/orkambicriteria.pdf>.
- 20 State of California—Health and Human Services Agency DoHCS. Lumacaftor/ivacaftor (Orkambi). N.L. 06-0915. 2015 Sep 4 [accessed 2017 Sep 1]. Available from: <http://www.dhcs.ca.gov/services/ccs/documents/ccsnl060915.pdf>.
- 21 Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 2016;316:858–871.
- 22 Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, *et al.* Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. *J Pediatr* 2017;181:S4–S15.e11.
- 23 Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, *et al.*; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–614.
- 24 Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjilias D, Hoag JB, *et al.*; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2013;187:680–689.
- 25 Lahiri T, Hempstead SE, Brady C, Cannon CL, Clark K, Condren ME, *et al.* Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. *Pediatrics* 2016;137:e20151784.
- 26 Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. *J Cyst Fibros* 2014;13:29–36.
- 27 Yu H, Burton B, Huang CJ, Worley J, Cao D, Johnson JP Jr, *et al.* Ivacaftor potentiation of multiple CFTR channels with gating mutations. *J Cyst Fibros* 2012;11:237–245.
- 28 De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, *et al.* Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros* 2014;13:674–680.
- 29 Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. *J Pediatr Psychol* 2003;28:535–545.
- 30 Cuppens H, Marynen P, De Boeck C, Cassiman J-J. Detection of 98.5% of the mutations in 200 Belgian cystic fibrosis alleles by reverse dot-blot and sequencing of the complete coding region and exon/intron junctions of the CFTR gene. *Genomics* 1993;18:693–697.
- 31 Kiewewetter S, Macek M Jr, Davis C, Curristin SM, Chu CS, Graham C, *et al.* A mutation in CFTR produces different phenotypes depending on chromosomal background. *Nat Genet* 1993;5:274–278.
- 32 Sheppard DN, Rich DP, Ostedgaard LS, Gregory RJ, Smith AE, Welsh MJ. Mutations in CFTR associated with mild-disease-form Cl<sup>-</sup> channels with altered pore properties. *Nature* 1993;362:160–164.
- 33 Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, *et al.*; VX11-770-110 (KONDUCT) Study Group. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *Lancet Respir Med* 2015;3:524–533.
- 34 Lukacs GL, Chang XB, Bear C, Kartner N, Mohamed A, Riordan JR, *et al.* The delta F508 mutation decreases the stability of cystic fibrosis transmembrane conductance regulator in the plasma membrane: determination of functional half-lives on transfected cells. *J Biol Chem* 1993;268:21592–21598.
- 35 Boyle MP, Bell SC, Konstan MW, McColley SA, Rowe SM, Rietschel E, *et al.*; VX09-809-102 Study Group. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *Lancet Respir Med* 2014;2:527–538.
- 36 Elborn JS, Ramsey BW, Boyle MP, Konstan MW, Huang X, Marigowda G, *et al.*; VX-809 TRAFFIC and TRANSPORT study groups. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *Lancet Respir Med* 2016;4:617–626.
- 37 Milla CE, Ratjen F, Marigowda G, Liu F, Waltz D, Rosenfeld M; VX13-809-011 Part B Investigator Group \*. Lumacaftor/ivacaftor in patients aged 6–11 years with cystic fibrosis and homozygous for F508del-CFTR. *Am J Respir Crit Care Med* 2017;195:912–920.
- 38 Hubert D, Chiron R, Camara B, Grenet D, Prévotat A, Bassinet L, *et al.* Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease. *J Cyst Fibros* 2017;16:388–391.
- 39 Corey M. Power considerations for studies of lung function in cystic fibrosis. *Proc Am Thorac Soc* 2007;4:334–337.
- 40 Davis PB, Byard PJ, Konstan MW. Identifying treatments that halt progression of pulmonary disease in cystic fibrosis. *Pediatr Res* 1997;41:161–165.
- 41 Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, *et al.* Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med* 2017;5:107–118.
- 42 Rosenfeld M, Allen J, Arets BH, Aurora P, Beydon N, Calogero C, *et al.*; American Thoracic Society Assembly on Pediatrics Working Group on Infant and Preschool Lung Function Testing. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc* 2013;10:S1–S11.
- 43 Aurora P, Stanojevic S, Wade A, Oliver C, Kozłowska W, Lum S, *et al.*; London Cystic Fibrosis Collaboration. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. *Am J Respir Crit Care Med* 2011;183:752–758.
- 44 Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, *et al.*; VX14-809-109 investigator group. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2017;5:557–567.