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Cystic Fibrosis Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis

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Abstract

Background: CFTR modulators are a new class of medications targeting the underlying defect in cystic fibrosis (CF). Ivacaftor (IVA) and IVA combined with lumacaftor (IVA/LUM) have been approved by the FDA for use in CF patients. 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.

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 Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, and recommendations were made based on this analysis.

Results: *F*or adults and children age 6 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 age 18 or older, and (2) children age 6-17 with an FEV1 <90% predicted. For those with the R117H mutation, the guideline panel made a conditional recommendation against treatment with IVA for (1) children age 12 to 17 with an FEV1 >90% predicted, and (2) children less than 6 years of age. Among those with two copies of

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F508del, the guideline panel made a strong recommendation for treatment with IVA/LUM for adults and children age 12 and older with an FEV1 <90% predicted; and made a conditional recommendation for treatment with IVA/LUM for (A) adults and children age 12 or older with an FEV1 > 90% predicted and (B) children age 6 to 11.

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.

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 CF patients with the G551D mutation [9]. The FDA approved IVA for CF patients aged ≥ 12 years with the G551D mutation in 2012. From 2013-2015, approval was expanded to include patients aged $\geq$ 6 years and those with other gating mutations. Even with the expanded indication, only about 10% of CF patients 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 CF patients 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

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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 CF patients homozygous for F508del demonstrated improved lung function and reduced pulmonary exacerbations [13]. In 2015, IVA/LUM was approved by the FDA for CF patients aged ≥ 12 years and homozygous for F508del. In 2016, FDA labelling was expanded to include patients aged ≥ 6 years.

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 pre-approval 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 CF patients' access to these medications (J Erdo, personal communication) [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 CF patient populations.

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

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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 CF patients. Clinicians, CF patients, and parents of CF patients will be able to use these recommendations when considering CFTR modulator therapy.

Methods

Definitions

For this guideline, the committee defined CF patients 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 (ETN and CLR) 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 conflict of interest 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, and effort for the

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methodologist, biostatistician, and clinical epidemiologist. The medical librarian was recruited from Indiana University, which did not charge any fees for her effort.

The committee used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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 while 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 Supplements.

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 CF patients aged ≥ 12 years who carry at least 1 copy of the G551D mutation or CF patients 2-5 years 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 CF patients with only 1

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 Supplements.

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 US 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 with these mutations in February, 2014 and extended this indication to individuals aged ≥ 2 years in March, 2015.

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Summary of the Evidence

Our search identified one randomized, placebo-controlled, crossover 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]. Thirty-nine patients aged 6 and older with a percent predicted forced expiratory volume in 1 second (PPFEV1) of 40% or greater were randomized to receive either IVA 150 mg every 12h 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 PPFEV1 improved among participants treated with IVA (13.76; 95% 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/m2 (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 PPFEV1, 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 PPFEV1 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 <2 years 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 <2 years the committee makes no recommendation, since at present there is no clinically available formulation or dosing information in this age range.

Recommendation 2: The committee suggests IVA for individuals with a diagnosis of CF aged 6-11 years with PPFEV1 < 40% and a gating mutation other than G551D or R117H. (Conditional recommendation, Very low certainty in the evidence).

Remarks: A patient with less than 40% FEV1 in this age group is presenting rapid progression of disease and the threshold to use therapies of potential benefit is lower. Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.

Recommendation 3: The committee suggests IVA treatment for individuals with a diagnosis of CF aged 6-11 years with PPFEV1 40%-90% and a gating mutation other than G551D or R117H (Conditional recommendation, Low certainty in the evidence).

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

Recommendation 4: The committee suggests IVA be used for individuals with a diagnosis of CF aged 6-11 years with PPFEV1 > 90% and a gating mutation other than G551D or R117H. (Conditional recommendation, Very low certainty in the evidence).

Remarks: Even though expected absolute change might be small, patients might be more likely to maintain FEV1 predicted. Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.

Recommendation 5: The committee suggests IVA for individuals with a diagnosis of CF aged 12-17 years with PPFEV1 < 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 ivacaftor may vary based on insurance coverage and cost to the patient.

Recommendation 6: The committee suggests IVA for individuals with a diagnosis of CF aged 12-17 years with PPFEV1 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 ivacaftor may vary based on insurance coverage and cost to the patient.

Recommendation 7: The committee suggests IVA for individuals with a diagnosis of CF aged 12-17 years with PPFEV1 > 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 ivacaftor may vary based on insurance coverage and cost to the patient.

Recommendation 8: The committee suggests IVA for individuals with a diagnosis of CF aged 18 years or older with PPFEV1 < 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 ivacaftor 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 PPFEV1 40%-90% and a gating mutation G551D or R117H (Conditional recommendation, Moderate certainty in the evidence).

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

Recommendation 10: The committee suggests IVA for individuals with a diagnosis of CF aged 18 years or older with PPFEV1 >90% and a gating mutation G551D or R117H (Conditional recommendation, Moderate certainty in the evidence).

Remarks: Decisions on whether or not to prescribe ivacaftor 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 quality of life and pulmonary exacerbations, and objective measures linked to mortality, such PPFEV1, and less value on the substantial expected costs of the therapy. The

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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. While patients with PPFEV1 < 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 PPFEV1. The available analysis did not stratify by age or PPFEV1 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 US 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 poly-thymidine 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]. Sixty-nine study subjects aged ≥ 6 years and with a PPFEV1 of ≥ 40% were randomized to receive either IVA 150 mg every 12h or placebo for 24 weeks. Randomization was stratified by age groups (6-11, 12-17, and ≥18 years), and PPFEV1 (< 70%, 70-90% and > 90%). For the entire population, the absolute mean difference in PPFEV1 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). Pre-specified subgroup analysis demonstrated an improvement in the mean difference of PPFEV1 in individuals aged ≥ 18 years vs. placebo (5.00; 95% CI: 4.25, 5.75), but not individuals aged 6-11 years (-6.30; 95% CI: -8.07, -4.53). Insufficient numbers of patients aged 12-17 precluded a separate subgroup analysis. Overall, the prevalence of 5T and 7T in the IVA group was 62% and 35% respectively, while in the placebo group it was 77% and 20%. Similar results were seen in both 5T and 7T study subjects.

Recommendation

Table 3 summarizes our recommendations for Question 2 stratified by age and PPFEV1, 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.

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Recommendation 11: The committee suggests against IVA therapy for individuals aged 0-5 and 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 was comprised of individuals aged 6-11 which contained few individuals with compromised lung function 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 disease, assessed by other criteria, is present.

Recommendation 12: The committee suggests IVA for individuals aged 6-11 years with PPFEV1 < 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 PPFEV1 40%-90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Very low certainty in the evidence).

Remarks: As above, 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 IVA not be used for individuals aged 6-11 years with PPFEV1 > 90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Low certainty in the evidence).

Remarks: The panel felt this group most closely matched the data from Moss, et al()which demonstrated a fall in ppFEV1 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 PPFEV1 < 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 PPFEV1 40%-90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Very low certainty in the evidence).

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

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Recommendation 17: The committee suggests against IVA for individuals aged 12-17 years with PPFEV1 > 90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Moderate certainty in the evidence).

Remarks: While data was limited for this age range, the panel felt this group most closely matched the data for the 6-11 group which demonstrated a fall in ppFEV1 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 PPFEV1 < 40% with a diagnosis of 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 PPFEV1 40%-90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Moderate certainty in the evidence).

Remarks: As above, 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 PPFEV1 >90% with a diagnosis of CF due to the R117H mutation (Conditional recommendation, Moderate certainty in the evidence).

Remarks: While 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 ivacaftor 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 PPFEV1 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 PPFEV1. The data available did stratify by age and PPFEV1 status but representation in each stratum varied widely. The younger patient cohort included very few individuals with low lung function and was over-represented by individuals with normal lung function, reducing the likelihood of substantial improvement from baseline. The aged ≥ 18 year age group had substantially more individuals with more severe airflow impairment and this group experienced more substantial improvement in PPFEV1, BMI and CFQ-R respiratory domain scores.

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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 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 sub-analysis, 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, while IVA improves its gating function [8,11].

Summary of the Evidence

Our search identified 4 papers in which IVA/LUM was used to treat CF patients homozygous for F508del: 3 reported results from three placebo-controlled RCTs [35-37] and one was an open-label extension study [38]. Wainwright et al [36] and Elborn et al [37] reported results from the same two RCTs. However, Elborn et al stratified analysis by PPFEV1, which complemented the results reported by Wainwright et al. Boyle et al included a cohort of patients heterozygous for F508del but only cohorts comprised of homozygous patients were included in their analysis [35]. When pooled, the RCTs included 1,268 patients aged ≥ 12 years and with PPFEV1 > 40%. Specific patient populations, medication doses, and duration of therapy varied among studies and among cohorts. The absolute mean difference in PPFEV1 improved for patients aged 12-17 years with baseline PPFEV1 40%-90% (3.06; 95% CI: 2.40, 3.72) and for patients aged $\underline{\geq}$ 18 years and PPFEV1 < 40%, 40%-90%, and > 90% (3.51; 95% CI: 3.01, 4.01; 3.92; 95% CI: 3.3, -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 groups with PPFEV1 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 $\underline{\geq}$ 18 with PPFEV1 > 90% (16.21; 95% CI: 13.05; 19.38). BMI improved in patients aged ≥ 12 years with PPFEV1 $\underline{\leq}$ 40% (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 with PPFEV1 40%-90% (RR 0.70; 95% CI: 0.66, 0.88 and RR 0.69; 95% CI: 0.56, 0.85).

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Recommendation

Table 4 summarizes our recommendations for Question 3 stratified by age and PPFEV1, 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 PPFEV1 <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 with a diagnosis of CF and two copies of the F508del mutation who are aged 6-11 years with PPFEV1 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 with a diagnosis of CF and two copies of the F508del mutation who are aged 6-11 years with PPFEV1 >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 PPFEV1. 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 with a diagnosis of CF and two copies of the F508del mutation who are aged 12-17 years with PPFEV1 <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 26: 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 PPFEV1 40%-90%. (Strong recommendation, Moderate certainty in the evidence).

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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 PPFEV1 >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 PPFEV1. 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 with a diagnosis of CF and two copies of the F508del mutation who are aged 18 years or older with PPFEV1 <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 with a diagnosis of CF and two copies of the F508del mutation who are aged 18

years or older with PPFEV1 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 with a diagnosis of CF and two copies of the F508del mutation who are aged 18 years or older with PPFEV1 >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 PPFEV1. 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 $\geq$ 12 years with baseline PPFEV1 $\leq$ 90% treated with combination IVA/LUM. For this reason, the committee made a strong recommendation for treatment with moderate certainty in the evidence. Patients with

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baseline PPFEV1 > 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. The open-label trial from Milla, et al [31] 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 PPFEV1. Another consideration in the decision to prescribed IVA/LUM is the reported increased incidence of cough and chest tightness among patients of all ages with PPFEV1 < 40% [39]. Patients have generally tolerated gradual reintroduction of therapy but early worsening of symptoms should be included in treatment discussions. Additionally, 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 on the Online Supplement.

Limitations and Future Directions

The available evidence for formulating this guideline was limited to 6 publications, 2 of which were analyses of the same study population and one of which was an open-label efficacy trial. While these clinical trials were well designed, the inclusion and exclusion criteria did not encompass the complete ranges of PPFEV1 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 PPFEV1, 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 uncertainly 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. Since CFTR modulators affect the fundamental defect in CF, they may also affect disease progression, which could be reflected in a lower rate of PPFEV1 decline. However, since the mean rate of PPFEV1 decline in CF patients is relatively small, a RCT powered to demonstrate a significant effect of CFTR modulators on PPFEV1 decline would either require very large

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numbers of study subjects or a long treatment period, rendering such a study very difficult to carry out [40,41]. One recent study, not considered by the committee because it was published after our search, did demonstrate a slower rate of PPFEV1 decline in individuals homozygous for F508del receiving IVA/LUM compared to a matched cohort from the CF Foundation Patient Registry [42]. However, since 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 recommendation to a strong one.

Data available for measurement of efficacy and formulation of the treatments considered in these guidelines was limited in younger age groups, especially in the 0-5 year age range. Young children <6 years old 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 [43], they are not widely used and have not been fully validated in CF research and clinical care. Moreover, PPFEV1 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 (ClinicalTrials.gov Identifier 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 [44], and IVA/LUM has been shown to increase PPFEV1 in children ages 6-11 years with CF and homozygous for the F508del mutation [45]. 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 above will be helpful for clinicians, patients, and their families in making current treatment decisions regarding CFTR modulators.

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Table 1. Interpretation of the strength of GRADE recommendations (adapted from ref [23]).

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 helping individuals making 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.

Table 2. Summary of Recommendations for PICO Question #1 (ivacaftor for CF patients due to gating mutations other than G551D or R117H.

Sub-group #	Age	PPFEV1	Certainty	Recommendation
1	2-5	N/A	N/A	Recommend for 2-5 years[1] No recommendation for <2 years
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

[1] Based on the CF Preschool Guidelines recommendations [25].

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Table 3. Summary of recommendations for PICO Question #2 (ivacaftor for CF patients with the R117H mutation).

Sub-group #	Age	PPFEV1	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

Table 4. Summary of recommendations for PICO Question #3 (ivacaftor/lumacaftor for CF patients with two copies of F508del)

Sub-group #	Age	PPFEV1	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

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Online Data Supplement

Cystic Fibrosis Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis

Clement L. Ren, Rebecca L. Morgan, Christopher Oermann, Helaine E. Resnick, Cynthia Brady, Annette Campbell, Richard DeNagel, Margaret Guill, Jeffrey Hoag, Andrew Lipton, Thomas Newton, Stacy Peters, Donna Beth Willey-Courand, Edward. T. Naureckas

Guidelines for the Use of CFTR Modulators in Patients with Cystic Fibrosis

Online Supplement: Detailed Recommendations

PICO Question 1:

Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 < 40% of predicted and a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT where IVA versus placebo was used 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 [1]. Thirty-nine patients aged 6 and older were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. No patients with a PPFEV1 < 40% were included in the study. The mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CF Questionnaire – Revised (CFQ-R) respiratory domain instrument [2], the mean difference was 12.82 (95% CI: 11.81, 13.83) higher for IVA versus placebo. BMI was improved in subjects treated with IVA by a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve statistical significance (risk ratio [RR] 0.80; 95% CI: 0.37, 1.70). 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).

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Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) for individuals aged 6-11 years with PPFEV1 < 40%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with more severe or more rapidly progressive disease may be more likely to value potential improvement in these outcomes. Patients with PPFEV1 < 40% were not included in the one RCT identified so the available evidence is very indirect in this subgroup. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations.

Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 40%-90% of predicted and a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of

40% or greater were randomized to receive either 150mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population, the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95%: CI 13.11; 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83; $p<0.05$). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44; 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve statistical significance (RR 0.80; 95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA treatment for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) for individuals aged 6-11 years with PPFEV1 40%-90%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with moderate to severe disease may be more likely to

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value potential improvement in these outcomes. The data available was not stratified by age and PPFEV1. While the PPFEV1 and age criteria of this group fall within the range of subjects recruited for this trial, the majority were older and a significant portion had PPFEV1 > 90% leading to indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more moderate to severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated, closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 > 90% of predicted and a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. There was no upper bound for PPFEV1. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For CFQ-R respiratory domain the mean difference

was 12.82 (95% CI: 11.81; 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance (RR 0.80; 95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA be used for individuals with a diagnosis of CF and a gating mutation G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D for individuals aged 6-11 years with PPFEV1 > 90%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease may place less value on potential improvement in these outcomes balanced against cost and potential side effects, though patients in this subgroup might benefit from a reduction in the rate of decline of their PPFEV1. The data within this study was not stratified by age and PPFEV1. While the PPFEV1 and age criteria of this group fall within the range of subjects recruited for this trial, the majority were older and had PPFEV1 < 90% which creates indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this

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medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 and with PPFEV1 < 40% of predicted and with a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. No patients with a PPFEV1 < 40% were included in the study; therefore, data from the entire trial with a mean PPFEV1 of 78.4% was used to inform these recommendations. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) aged 12-17 years with PPFEV1 < 40%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy Patients with more severe or more rapidly progressive disease may be more likely to value potential improvement in these outcomes. Patients with PPFEV1 < 40% were not included in the one RCT identified so the available evidence is very indirect in this subgroup. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. Patients with PPFEV1 < 40% were not included in the one RCT identified so that the evidence from that trial remains indirect in this subgroup. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more severe disease is present.

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Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 and with PPFEV1 40%-90% of predicted and with a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D)

aged 12-17 years with PPFEV1 40%-90%. (Conditional recommendation, Moderate certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with moderate to severe disease may be more likely to value potential improvement in these outcomes. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. The group mean for PPFEV1 was also contained within this subgroup reducing the degree of indirectness of the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more moderate to severe disease is present.

Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 with PPFEV1 > 90% of predicted and a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 8

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weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) aged 12-17 years with PPFEV1 > 90%. (Conditional recommendation, Moderate certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease may place less value on potential improvement in these outcomes balanced against cost and potential side effects. The

data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. While there was no upper bound in PPFEV1 the majority of subjects had a PPFEV1 < 90% which creates indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged ≥18 with PPFEV1 < 40% of predicted and with a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. No patients with a PPFEV1< 40% were included in the study. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference

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of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) aged 18 years or older with PPFEV1 < 40%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease might place less value on potential improvement in these outcomes balanced against cost and potential side effects. The data available were not stratified by age and PPFEV1 status but the ages included in this include the group mean. Patients with more severe or more rapidly progressive disease may be more likely to value potential improvement in these outcomes. Patients with PPFEV1 < 40% were not included in the one RCT identified so that the evidence from that trial remains indirect in this subgroup. The overall consensus of the group was that patients, and providers would be likely to use this medication in most situations where more severe disease is present.

Should ivacaftor versus no CFTR treatment be used for individuals aged ≥18 with PPFEV1 40-90% of predicted and with a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R respiratory domain, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The CFTR modulator guidelines panel suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D)

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aged 18 years or older with PPFEV1 40%-90%. (Conditional recommendation, Moderate certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with more moderate to severe disease may be more likely to value potential improvement in these outcomes. The data available were not stratified by age and PPFEV1 status but the age range of this subgroup included the group mean. The group mean for PPFEV1 was also contained within this subgroup, reducing the degree of indirectness of the evidence. The overall consensus of the group was that patients and providers would be likely to use this medication in most situations where more moderate to severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged ≥ 18 with PPFEV1 > 90% of predicted and with a CF diagnosis due to gating mutations other than G551D or R117H mutations?

Summary of the evidence:

Our search yielded one RCT versus placebo where IVA was used 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 [1]. Thirty-nine patients aged 6 and older and a PPFEV1 of

40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 8 weeks. Subjects were then crossed over to the alternate treatment arm, placebo or IVA, for an additional 8 weeks. The initial phase of the study was followed by an open label phase where all patients received IVA for an additional 16 weeks. For the entire population the mean difference in PPFEV1 between IVA and placebo therapy was 13.76 (95% CI: 13.11, 14.41). For the CFQ-R, the mean difference was 12.82 (95% CI: 11.81, 13.83). BMI was improved in subjects treated with IVA with a mean difference of 0.66 kg/m2 (95% CI: 0.44, 0.88). The number of exacerbations in patients receiving IVA was reduced but did not achieve significance RR 0.80 (95% CI: 0.37, 1.70). 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).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and a gating mutation (G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D) aged 18 years or older with PPFEV1 >90%. (Conditional recommendation, Moderate certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease my place less value on potential improvement in these outcomes balanced against cost and potential side effects. The

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data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. While there was no upper bound in PPFEV1 the majority of subjects had a PPFEV1 < 90% which retains some degree of indirectness in the evidence. The overall consensus of the group was that patients and providers would be likely to use this medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

PICO Question 2:

Should ivacaftor versus no CFTR treatment be used for individuals aged 0-5 and a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded no RCTs including patients in this age group. We were able to identify one study where IVA was used for the treatment of patients with CF and a copy of the R117H mutation [3]. Sixty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Pre-specified subgroup analysis for patients aged 6-11 years demonstrated no improvement in PPFEV1 and a small reduction in airflow (-6.3; 95% CI: -8.07, -4.53), as well as decreased quality of life (-6.1; 95% CI: -9.01, -3.19). Results were not stratified by Poly-T status and approximately equal numbers of individuals with 5T and 7T status were represented in the aged 6-11 years group. While stratified to a matching age group, the committee felt that the data was indirect for individuals aged 0-5 years that the group mean and the stratified results for individuals aged $\geq$18 years of age should also be considered. For the overall group, PPFEV1 was demonstrated an improvement, although not statistically significant (2.1; 95% CI: -1.56, 2.64). For CFQ-R respiratory domain, the difference was 8.4 (95% CI: 7.36, 9.44). There were small, non-significant changes in body mass index as well (mean difference 0.36; 95% CI: -0.05, 0.57).

Recommendation:

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The committee suggests against the use of IVA for individuals with a diagnosis of CF and an R117H mutation aged 0-5 years (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The overall consensus of the group was that parents and providers would be unlikely to use this medication in children with few symptoms and minimal disease. However, given the high variability of disease severity, providers and families may still consider the use of this medication where more severe disease, more rapidly progressive disease, or more frequent exacerbations are present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated, closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 < 40% of predicted and a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT placebo trial where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Pre-specified subgroup analysis for patients aged 6-11 years demonstrated no

improvement in PPFEV1 and a small reduction in airflow (-6.3; 95% CI: -8.07, -4.53), as well as decreased quality of life (-6.1; 95% CI: -9.01, -3.19). Results were not stratified by Poly-T status and approximately equal numbers of individuals with 5T and 7T status were represented in the aged 6-11 years group. While stratified to a matching age group, the committee felt that the data was indirect for individuals in this range of lung function and that the group mean and the stratified results for individuals aged ≥18 years of age should also be considered. For the overall group, PPFEV1 was demonstrated an improvement, although not statistically significant (2.1; 95% CI: -1.56, 2.64). For CFQ-R respiratory domain, the difference was 8.4 (95% CI: 7.36, 9.44). There were small, non-significant changes in body mass index as well (mean difference 0.36; 95% CI: -0.05, 0.57).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 6-11 years with PPFEV1 < 40%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although, the balance between these values will vary widely among patients with R117H, patients in this age range with severe disease already present likely represent individuals for whom treatment would be favored. The data available did

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stratify by age and PPFEV1 status but the strata representing individuals aged 6-11 years contained very few individuals with compromised lung function, providing less likelihood of substantial improvement from baseline as well as possible over-representation of individuals with limited disease penetrance. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care.

Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 40-90% of predicted and a CF diagnosis due to the R117H mutation?

Summary of the evidence:

The evidence considered was the same as for individuals with PPFEV1< 40%. Our search yielded one RCT where IVA was used for the treatment of patients with CF and a copy of the R117H mutation [3]. Sixty-nine patients aged 6 years and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Pre-specified subgroup analysis for patients aged 6-11 years demonstrated no improvement in PPFEV1 and a small reduction in airflow (-6.3; 95% CI: -8.07, -4.53), as well as decreased quality of life (-6.1; 95% CI: -9.01, -3.19). Results were not stratified by Poly-T status and approximately equal numbers of individuals with 5T and 7T status were represented in the aged 6-11 years group. While stratified to a matching age group, the committee felt that the data was indirect for individuals in this range of lung function and the stratified results for individuals aged $\geq$18 years of age should also be considered. For the overall group, PPFEV1 was demonstrated an

improvement, although not statistically significant (2.1; 95% CI: -1.56, 2.64). For CFQ-R respiratory domain, the difference was 8.4 (95% CI: 7.36, 9.44). There were small, non-significant changes in body mass index as well (mean difference 0.36; 95% CI: -0.05, 0.57).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 6-11 years with PPFEV1 40%-90%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H and likely reflect relative lung function. The data available did stratify by age and PPFEV1 status but the strata representing individuals aged 6-11 contained very few individuals with compromised lung function providing less likelihood of substantial improvement from baseline as well as possible over-representation of individuals with limited disease penetrance. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care.

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Should ivacaftor versus no CFTR treatment be used for individuals aged 6-11 with PPFEV1 > 90% of predicted and a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 years and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Pre-specified subgroup analysis for patients aged 6-11 years (17 patients) demonstrated no improvement in PPFEV1 and, in fact, demonstrated a small reduction in airflow (mean difference -6.3; 95% CI: -8.07, -4.53). The mean PPFEV1 for patients receiving IVA in this age stratum at baseline was 97% (SD: 8.6), which demonstrated a higher degree of directness for patients with higher lung function than for patients with lower lung function. The mean quality of life based on the respiratory domain of the CFQ-R respiratory domain decreased (-6.1; 95% CI: -9.01, -3.19). Small, not statistically significant decreases in BMI where noted as well in this pre-specified sub analysis (mean difference -0.18; 95% CI: -0.92, 0.56).

Recommendation:

The committee suggests against to use of IVA for individuals with a diagnosis of CF and an R117H mutation aged 6-11 with PPFEV1 >90%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The available data stratified by age and PPFEV1 status were more closely matched within this subgroup than for those with more severely reduced lung function. The overall consensus of the group was that patients, parents, and providers would be much less likely to use this medication in this situation, but that providers and families may still consider the use of this medication where more rapidly progressive disease is present, there are frequent exacerbations, or patients have lower baseline lung function. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 and with PPFEV1 < 40% of predicted and with a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT placebo trial where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and > 90%. Only two patients aged 12-17 years were included in the study and a sub-analysis for this group was not performed. For this reason, data for the group mean was considered as well as data from individuals aged >18 years, which, while more indirect in terms of age, was more direct with respect to baseline lung function. This group demonstrated an

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improvement in mean PPFEV1 function (2.1; 95% CI: 1.56, 2.64). A significant improvement in the respiratory domain of the CFQ-R respiratory domain was also observed (8.4; 95% CI: 7.36, 9.44).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 12-17 years with PPFEV1 < 40%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although, the balance between these values will vary widely among patients with R117H, patients in this age range with severe disease already present likely represent individuals for whom treatment would be favored. The data available did stratify by age and PPFEV1 status but the stratum representing individuals aged 12-17 years contained only two individuals. The overall consensus of the group was that most patients, parents, and providers would be likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.

Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 and with PPFEV1 40%-90% of predicted and with a CF diagnosis due to the R117H mutation?

Summary of the evidence:

The evidence considered was the same as for individuals with PPFEV1< 40%. Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation (Moss 2015). Sixty-nine patients aged 6 and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and > 90%. Only two patients aged 12-17 years were included in the study and a sub-analysis for this group was not performed. For this reason data for the group mean were considered as well as for individuals aged >18 years, which, while more indirect in terms of age, was more direct with respect to baseline lung function. This group demonstrated an improvement in mean PPFEV1 function (2.1; 95% CI: 1.56, 2.64). A significant improvement in the respiratory domain of the CFQ-R respiratory domain was also observed (8.4; 95% CI: 7.36, 9.44).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation in for individuals aged 12-17 years with PPFEV1 40-90%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial

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expected costs of the therapy. The balance between these values will vary widely among patients with R117H and likely reflect relative lung function. The data available did stratify by age and PPFEV1 status but the strata representing individuals aged 12-17 years contained only two individuals. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care.

Should ivacaftor versus no CFTR treatment be used for individuals aged 12-17 with PPFEV1 > 90% of predicted and a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 and older with a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and >90%. Only two patients aged 12-17 years were included in the study and a sub-analysis for this group was not performed. For this reason data for the group mean were considered as well as for individuals aged >18 years, which, while more indirect in terms of age, was more direct with respect to baseline lung function. This group demonstrated an improvement in mean PPFEV1 function (2.1; 95% CI: 1.56, 2.64). A significant improvement in the respiratory domain of the CFQ-R respiratory domain was also observed (8.4; 95% CI: 7.36, 9.44).

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Recommendation:

The committee suggests against the use of IVA for individuals with a diagnosis of CF and an R117H mutation aged 12-17 years with PPFEV1 > 90%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The data available, stratified by PPFEV1 status, were more closely matched within this subgroup than for those with more severely reduced lung function. The overall consensus of the group was that patients and providers would be much less likely to use this medication in this situation but that providers, parents, and families may still consider the use of this medication where more rapidly progressive disease is present or frequent exacerbation are present or patients with an PPFEV1 at the lower end of this range (closer to 90%). The high cost of the medication may also limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

Should ivacaftor versus no CFTR treatment be used for individuals aged ≥18 with PPFEV1 < 40% of predicted and with a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 years and older and a PPFEV1 of

40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and > 90%. Data from individuals aged >18 years with any PPFEV1 level was considered, which was still somewhat indirect with respect to baseline lung function. The pre-specified sub-group analysis demonstrated an improvement in PPFEV1 versus placebo (5.0; 95% CI: 4.25, 5.75). A significant improvement in the CFQ-R respiratory domain was also observed (12.7; 95% CI: 11.23, 14.17).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 18 years or older with PPFEV1 < 40%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H due to the high variability of clinical outcomes in individuals with this mutation, but patients with severe disease already present would represent those for whom treatment would be favored. The data was stratified for this age group. The overall consensus of the group was that patients and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.

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Should ivacaftor versus no CFTR treatment be used for individuals aged ≥ 18 with PPFEV1 40-90% of predicted and with a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 years and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and > 90%. Data from individuals aged >18 years with any PPFEV1 level was considered. The pre-specified sub-group analysis demonstrated an improvement in PPFEV1 versus placebo (5.0; 95% CI: 4.25, 5.75). A significant improvement in the respiratory domain of the CFQ-R was also observed (12.7; 95% CI: 11.23, 14.17).

Recommendation:

The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 18 years or older with PPFEV1 40%-90%. (Conditional recommendation, Moderate certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among

patients with R117H and likely reflect relative lung function. The overall consensus of the group was that patients and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.

Should ivacaftor versus no CFTR treatment be used for individuals aged ≥ 18 with PPFEV1 > 90% of predicted and with a CF diagnosis due to the R117H mutation?

Summary of the evidence:

Our search yielded one RCT where IVA was used for the treatment of patients with CF with a copy of the R117H mutation [3]. Sixty-nine patients aged 6 years and older and a PPFEV1 of 40% or greater were randomized to receive either 150 mg IVA or placebo every 12 hours for 24 weeks. Randomization was stratified by age groups: 6-11, 12-17, and 18 and above and PPFEV1 < 70%, 70%-90% and > 90%. Data from individuals aged >18 years with any PPFEV1 level was considered, which was still somewhat indirect with respect to baseline lung function. The pre-specified sub-group analysis demonstrated an improvement in PPFEV1 versus placebo (5.0; 95% CI: 4.25, 5.75). A significant improvement in the respiratory domain of the CFQ-R was also observed (12.7; 95% CI: 11.23, 14.17).

Recommendation: The committee suggests IVA for individuals with a diagnosis of CF and an R117H mutation aged 18 years or older with PPFEV1 > 90%. (Conditional recommendation, Low certainty in the evidence).

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Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H due to the high variability of clinical outcomes in individuals with this mutation. The overall consensus of the group was that patients and providers would be more likely to use this medication in situations where more symptomatic, more rapidly progressive disease or with a PPFEV1 at the lower end of this range (close to 90%), but would be less likely to use this therapy for more stable or minimal disease within this subgroup. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

PICO Questions for Question 3

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 6-11 years and PPFEV1 < 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

There are no RCTs assessing the safety and efficacy of IVA/LUM combination therapy in children age 6-11 years, and efficacy data are not required to obtain an FDA indication for this age group if the efficacy data from older patients can be extrapolated to younger patients [4]. Safety has been assessed in a 24-week, open-label, Phase 3 study including 58 patients age 6-11 years [5]. The authors report that combination therapy was well tolerated, with a safety profile similar to that seen in older patients who participated in larger studies. Ventilation inhomogeneity, as measured by the lung clearance index, was also improved at the end of the open-label treatment period. Milla, et al included an indirect population of healthier participants with a mean PPFEV1 of 91.4 (SD: 13.7) [5]. To determine the relative effect of IVA/LUM versus placebo, we compared Milla, et al against a historical control of persons with the same CF mutation who received placebo in a randomized controlled trial [6]. This comparison suggested improvements among persons receiving IVA/LUM in pulmonary function (2.9; 95% CI: 0.26, 5.54), quality of life using the CFQ-R respiratory domain (4.5; 95% CI: 0.58, 8.42), and nutritional status (0.54; 95% CI: 0.36, 0.72). Participants receiving IVA/LUM reported reduction in pulmonary exacerbations (RR 0.43; 95% CI: 0.26, 0.72) and lower respiratory symptoms (RR 0.24; 95% CI: 0.14, 0.40).

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Recommendation:

The committee suggests IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 6-11 years with PPFEV1 less than 40%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there are no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the committee elected to make a conditional recommendation for therapy. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. Other considerations may include cost, convenience, and the potential for unknown adverse effects.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 6-11 years and PPFEV1 40%-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

There are no RCTs assessing the safety and efficacy of IVA/LUM combination therapy in children age 6-11 years , and efficacy data are not required to obtain an FDA indication for this age group if the efficacy data from older patients can be extrapolated to younger patients [4]. Safety has been assessed in a 24-week, open-label, Phase 3 study including 58 patients age 6-11 years [5]. The authors report that combination therapy was well tolerated, with a safety profile similar to that seen in older patients who participated in larger studies. Ventilation inhomogeneity, as measured by the lung clearance index, was also improved at the end of the open-label treatment period. Milla, et al included an indirect population of healthier participants with a mean PPFEV1 of 91.4 (SD: 13.7) [5]. To determine the relative effect of IVA/LUM versus placebo, we compared Milla, et al against a historical control of persons with the same CF mutation who received placebo in a randomized controlled trial [6]. This comparison suggested improvements among persons receiving IVA/LUM in pulmonary function (2.9; 95% CI: 0.26, 5.54), quality of life using the CFQ-R respiratory domain (4.5; 95% CI: 0.58, 8.42), and nutritional status (0.54; 95% CI: 0.36, 0.72). Participants receiving IVA/LUM reported reduction in pulmonary exacerbations (RR 0.43; 95% CI: 0.26, 0.72) and lower respiratory symptoms (RR 0.24; 95% CI: 0.14, 0.40).

Recommendation:

The committee suggests IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 6-11 years and PPFEV1 40%-90%. (Conditional recommendation, Very low certainty in the evidence).

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Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there are no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the committee elected to suggest therapy based on a conditional recommendation. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. In other age groups, patients with better maintained lung function (PPFEV1 > 90%) did not experience the same relative benefit as those with lower lung function. Providers and families may take this into consideration discussing potential therapies. Other considerations may include cost, convenience, and the potential for unknown adverse effects.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 6-11 years and PPFEV1 > 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

There are no RCTs assessing the safety and efficacy of IVA/LUM combination therapy in children age 6-11 years, and efficacy data are not required to obtain an FDA indication for this age group if the efficacy data from older patients can be extrapolated to younger patients [4]. Safety has been assessed in a 24-week, open-label, Phase 3 study including 58 patients age 6-11 years [5].

The authors report that combination therapy was well tolerated, with a safety profile similar to that seen in older patients who participated in larger studies. Ventilation inhomogeneity, as measured by the lung clearance index, was also improved at the end of the open-label treatment period. To determine the relative effect of IVA/LUM versus placebo, we compared Milla, et al against a historical control of persons with the same CF mutation who received placebo in a randomized controlled trial [6]. This comparison suggested improvements among persons receiving IVA/LUM in pulmonary function (2.9; 95% CI: 0.26, 5.54), quality of life using the CFQ-R respiratory domain (4.5; 95% CI: 0.58, 8.42), and nutritional status (0.54; 95% CI: 0.36, 0.72). Participants receiving IVA/LUM reported reduction in pulmonary exacerbations (RR 0.43; 95% CI: 0.26, 0.72) and lower respiratory symptoms (RR 0.24; 95% CI: 0.14, 0.40).

Recommendation:

The committee suggests IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 6-11 years and PPFEV1 greater than 90%. (Conditional recommendation, Very low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there is no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the

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committee elected to suggest therapy based on a conditional recommendation. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. In other age groups, patients with better maintained lung function (PPFEV1 > 90%) did not experience the same relative benefit as those with lower lung function. Providers and families may take this into consideration when engaged in co-production for disease management. Other considerations may include cost, convenience, and the potential for unknown adverse effects.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 12-17 years and PPFEV1 < 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

Two RCTs included data on patients age 12-17 years and PPFEV1 < 40% [6,7]. Meta-analysis included 53 and 56 patients in the treatment and placebo groups respectively. The mean difference in PPFEV1 between groups was 3.51 (95% CI: 3.01, 4.01), with improvement favoring the treatment group. Nutritional status as measured by BMI was also significantly improved in the treatment group, with an increase of 0.46 (95% CI: 0.38, 0.53). Changes in upper and lower respiratory symptoms, cough, pulmonary exacerbation, CFQ-R respiratory domain, and adverse events and serious adverse events did not differ significantly between groups.

Recommendation:

The committee recommends IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 12-17 years with PPFEV1 less than 40%. (Strong recommendation, Moderate certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although the two trials had very large numbers of participants, there were relatively few patients age 12-17 years. Nonetheless, the committee felt that the numbers were sufficient to suggest a moderate degree of certainty of moderate benefit, warranting a strong recommendation for therapy. Another important consideration was the potential for long term stabilization of lung function. The prognosis for a patient age 12-17 years with PPFEV1 < 40% is not good. The committee felt, once again, that short term improvements in PPFEV1 and BMI, though perhaps not clinically significant, suggested that significant long term benefits were likely and that the balance between desirable and undesirable effects favored treatment. The committee did note, however, that there are anecdotal reports of increased cough and chest tightness among patients of all ages with PPFEV1 < 40%.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 12-17 years and PPFEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

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Summary of the evidence:

Meta-analysis of two RCTs included data on patients (1399 treatment and 1402 placebo) age 12-17 years with PPFEV1 40-90% [6,7]. Improvement in PPFEV1 mean difference favored the treatment group by 3.06 (95% CI: 2.40, 3.72). Other outcomes with improvement favoring treatment included decreased cough (RR 0.74; 95% CI: 0.62, 0.90), pulmonary exacerbation (RR 0.76; 95% CI: 0.66, 0.88), and serious adverse event (RR 0.70; 95% CI: 0.54, 0.91), as well as mean difference improvements in quality of life as demonstrated by the CFQ-R respiratory domain score (2.61; 95% CI: 1.63, 3.59) and BMI (0.27; 95% CI 0.13, 0.40). There were no significant differences in upper or lower respiratory symptoms.

Recommendation:

The committee recommends IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 12-17 years with PPFEV1 40%-90%. (Strong recommendation, Moderate certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Very large numbers of patients age 12-17 years with PPFEV1 40-90% were included in the two trials. Clinically-important improvements were noted in most patient-important clinical outcomes. Hence, the committee felt that there was a moderate degree of certainty of moderate benefit. A relatively low degree of concern regarding potential

adverse effects resulted in a strong recommendation for therapy. Of course, decisions to treat individual patients must be based upon patient-specific factors. Considerations should include PPFEV1 (there may be a greater rationale to treat a patient with PPFEV1 of 40% compared to a patient with PPFEV1 of 90%), comorbidities (e.g. liver disease), patient/family desires (co-production), and concerns over potential adverse effects.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age 12-17 years and PPFEV1 > 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

Neither of the published RCTs included patients age 12-17 years with PPFEV1 > 90%. Hence, no direct evidence was available for consideration when making a recommendation. Recommendations were made by the committee considering other PPFEV1 groups in this age range and adult patients with a PPFEV1 of > 90%. Improvement in PPFEV1 mean difference favored the treatment group by 3.06 (95% CI: 2.40, 3.72). Other outcomes with improvement favoring treatment included decreased cough (RR 0.74; 95% CI: 0.62, 0.90), pulmonary exacerbation (RR 0.76; 95% CI: 0.66, 0.88), and serious adverse event (RR 0.70; 95% CI: 0.54, 0.91), as well as mean difference improvements in quality of life as demonstrated by the CFQ-R respiratory domain score (2.61; 95% CI: 1.63, 3.59) and BMI (0.27; 95% CI 0.13, 0.40). There were not significant differences in upper or lower respiratory symptoms.

Recommendation:

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The committee suggests IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 12-17 years with PPFEV1 greater than 90%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations:

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. As above, there is no data directly informing a decision to treat patients age 12-17 years and PPFEV1 > 90%. However, extrapolation of data from patients in this age group with lower PPFEV1 and adult patients with PPFEV1 > 90% led the committee to suggest treatment rather than no treatment for these patients. The committee believed that there is no reason for patients meeting these demographic criteria to respond differently to treatment than similar patients of different ages or with lower PPFEV1. Additionally, the committee believed that a low level of concern regarding potential adverse effects favored treatment in the light of the known disease severity of the homozygous F508del genotype. Lastly, the potential for long term treatment with combination IVA/LUM to decrease the rate of decline of PPFEV1 suggests that patients age 12-17 years and PPFEV1 > 90% will benefit from therapy [8].

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age ≥ 18 and PPFEV1 < 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

Two RCTs included patients age 18 years and older with a PPFEV1 < 40% [6,7]. Meta-analysis included 53 and 56 patients in the treatment and placebo groups respectively. The mean difference in PPFEV1 between groups was 3.51 (95% CI: 3.01, 4.01), with improvement favoring

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the treatment group. BMI was also significantly improved in the treatment group, with an increase of 0.46 (95% CI: 0.38, 0.53). Changes in upper and lower respiratory symptoms, cough, pulmonary exacerbation, health-related quality of life, and adverse events and serious adverse events did not differ significantly between groups.

Recommendation:

The committee recommends IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 18 years and older with PPFEV1 less than 40%. (Strong recommendation, Moderate certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although the two RCTs had very large numbers of participants, there were relatively few patients age 18 years and older with a PPFEV1 < 40%. Nonetheless, the committee felt that the numbers were sufficient and there was enough generalizable data (from other age and PPFEV1 groups) to suggest a moderate degree of certainty of moderate benefit, warranting a strong recommendation for therapy. As with younger patients with significant disease burden, the committee believed that potential long term benefits outweigh potential adverse effects. The committee did note, however, that there are anecdotal reports of increased cough and chest tightness among patients of all ages with PPFEV1 < 40%. Consideration should be given to this and other potential issues prior to initiation of therapy.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age ≥ 18 and PPFEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

Three RCTs provided data from patients 18 years and older with a PPFEV1 of 40-90% receiving combination IVA/LUM therapy (n = 798) versus placebo (n= 408) [6,7,9]. Meta-analyses demonstrated an improvement among the treatment arm in mean difference in PPFEV1 (3.92; 95% CI: 3.33, 4.52), quality of life as measured by the CFQ-R respiratory domain scale (7.33; 95% CI: 5.95, 8.71), and BMI (0.27; 95% CI: 0.13, 0.40). Significant decreases were reported for lower respiratory symptoms (RR 0.90; 95% CI: 0.82, 0.98); pulmonary exacerbations (RR 0.76; 95% CI: 0.66, 0.88), and serious adverse events (RR 0.69; 95% CI: 0.56, 0.85). There were not significant differences in upper respiratory symptoms between treatment and control arms.

Recommendation:

The committee recommends IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 18 years and older with PPFEV1 40%-90%. (Strong recommendation, Moderate certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The majority of patients in the three RCTs comparing treatment

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with the IVA/LUM combination drug versus no treatment were age 18 years and older with a PPFEV1 of 40-90%. Compelling evidence from these three trials demonstrates significant improvements in several patient-important clinical outcomes. The committee judged the clinical benefit to patients to be moderate to large with a moderate degree of certainty leading to a strong recommendation. The risk of adverse effects was felt to be small though there were some concerns raised. These included drug-drug interactions, impact of IVA/LUM on birth control, and potential unidentified long term adverse effects (e.g. liver disease). Consideration was also given to preliminary reports suggesting that the rate of decline of PPFEV1 may be decreased in patients treated with IVA/LUM. This suggests potential long term benefit and increases the benefit to risk ratio.

Should chronic treatment with the ivacaftor/lumacaftor combination drug versus no treatment, be used in individuals age ≥ 18 and PPFEV1 > 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

Summary of the evidence:

A single RCT included patients age 18 years and older with PPFEV1 > 90% [9]. Meta-analysis including 89 patients treated with IVA/LUM and 117 receiving placebo demonstrated a mean difference in favor of treatment in PPFEV1 (5.59; 95% CI: 3.24, 7.94) and quality of life (16.21; 95% CI: 13.05; 19.38). There were not significant differences between treatment and placebo groups for upper and lower respiratory symptoms, pulmonary exacerbation, adverse events, or serious adverse events. BMI was not measured in this trial.

Recommendation:

The committee suggests IVA/LUM combination drug for individuals with a diagnosis of CF and two copies of the F508del mutation aged 18 years and older with PPFEV1 greater than 90%. (Conditional recommendation, Low certainty in the evidence).

Justification and implementation considerations.

This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The committee acknowledged very indirect evidence for the benefit of treatment with IVA/LUM for patients age 18 years and older with PPFEV1 > 90%. This resulted in low certainty regarding benefits and a conditional recommendation. Additional factors in this decision included cost/benefit considerations and potential issues with drug-drug interaction, birth control, and possible long term adverse effects (liver disease). Another important discussion point was whether an adult population with normal lung function would desire initiation of a very costly therapy, particularly in light of possible complicating issues as just described. A decision to start therapy would clearly require discussion between patient and provider. Thus, the committee elected to suggest rather than recommend treatment. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.

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Recommendation 1

Should **ivacaftor** vs. **no treatment** be used for **individuals age 0-5 years with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 0-5 years with a diagnosis of CF with mutations other than G551D and R117H
INTERVENTION:	ivacaftor
COMPARISON:	no treatment
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1; Pulmonary function as measured by relative change in percent predicted FEV1; Frequency of Exacerbation; Adverse Events; Respiratory Symptoms; Cough; Quality of Life; Nutritional Status (BMI); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score;
SETTING:	Outpatient
PERSPECTIVE:	Population

BACKGROUND:

CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient.

The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR.

IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ○ Yes	**Research evidence:** Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of

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	○ Varies ○ Don't know	the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Research evidence:** No randomized controlled trials were identified for persons under 5 years of age with mutations other than G551D comparing treatment with ivacaftor vs placebo. The KIWI trial evaluated the use of ivacaftor in persons 2–5 years old with the G551D gating mutation (Davies et al., 2016).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	

VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The price of ivacaftor is in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41) and Flume (1.72; 95% CI: 1.31, 2.13). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. Additionally, the panel determine that the cost-effectiveness may favors the intervention because of downstream costs prevented (lung transplant, etc.); however, the cost-effectiveness may also favor the comparison based on the cost and sensitivity, if the modeled assumptions were altered to directly address this PICO. After two rounds of voting the panel decided that the cost-effectiveness varies. The panel would like this decision to be made by the practitioner to consider unique patient needs.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

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Conclusions

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The CFTR guideline panel will defer to preschool guidelines for 2-5 years with gating mutations other than G551D/R117H. The panel expects that new evidence will be available for this age group based on the results of an on-going study (i.e., further studies may alter this recommendation) and refer to infant guidelines until new evidence is available.				
JUSTIFICATION	Panel discussed and needs more consideration given the age groups, evidence, current consensus recommendations address 2-5 age group. The panel agreed to defer to the preschool guidelines for persons age 2-5 with CF with gating mutations other than G551D and R117H (9 in favor; 3 absent). Regarding persons age 0-2 years, the panel recognized limited safety data and dosing recommendations for ivacaftor. The panel expects that new evidence will be available for this age group based on the results of an on-going study (i.e., further studies may alter this recommendation) and refer to infant guidelines until new evidence is available (9 in favor; 3 absent).				
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.				
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.				

MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E. Long-term follow up studies needed to examine lung function and exacerbation.

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Recommendation 2

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5); Upper respiratory symptoms; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse events - Ivacaftor 150 mg BID; Any adverse events - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients with CF mutation other than G551D or R117H with FEV1 less than 40%. One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (De Boeck et al., 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation</td><td>75
(1 RCT)</td><td>⨁◯◯◯
VERY LOW[a b]</td><td>RR 0.80
(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>297 per 1,000</td><td>59 fewer per 1,000
(187 fewer to 208 more)</td></tr>
<tr><td>Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4)
Scale from: 0 to 100
follow up: mean 08 weeks</td><td>74
(1 RCT)</td><td>⨁⨁◯◯
LOW[b]</td><td>-</td><td>The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) was 0</td><td>MD 12.82 higher
(11.81 higher to 13.83 higher)</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

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Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 40 follow up: mean 8 weeks	74 (1 RCT)	⊕⊕◯◯ LOW[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕◯◯◯ VERY LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse events - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕◯◯◯ VERY LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Any adverse events - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕◯◯◯ VERY LOW[b c]	**RR 0.88** (0.69 to 1.11)	Study population	
				838 per 1,000	**101 fewer per 1,000** (260 fewer to 92 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: mean 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[b]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

a. 95% CI includes line of no effect. Few events.
b. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

		c. 95% CI includes line of no effect. **Additional considerations:** All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to use indirect evidence from persons age 6-11 with FEV1 greater than 40%, the panel discussed that persons age 6-11 with FEV1 less than 40% might experience the same degree of potential benefit from treatment with ivacaftor. The panel agreed about the indirectness of informing this guideline question with evidence from De Boeck et al. 2014, as the study does not include FEV1 < 40% for this age group. One concern of using this evidence to inform recommendations for persons at lower lung function is that treatment might not be able to fix impact on lung function and there may be more atypical disease course. Imprecision was recognized for the outcomes of serious adverse events and pulmonary exacerbations. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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	variability ○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Research evidence:** Research evidence from De Boeck et al., 2014 was considered. **Additional considerations:** The panel decided that the balance of desirable and undesirable effects is in favor of the treatment intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc. **Additional considerations:** The panel agreed with price quoted.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:**

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	● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR modulator guideline panel suggests ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation; Very low certainty in the evidence*				

	Remarks: -A patient with less than 40% FEV1 in this age group is presenting rapid progression of disease and may benefit from more aggressive intervention. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with more severe or more rapidly progressive disease may be more likely to value potential improvement in these outcomes. Patients with PPFEV1 < 40% were not included in the one RCT identified so the available evidence is very indirect in this subgroup. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions.

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Evidence Profile for Recommendation 2

Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation												
1	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: mean 08 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	very serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⨁⨁◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: mean 8 weeks; Scale from: 0 to 40)												
1	randomized trials	not serious	not serious	very serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕◯◯◯ VERY LOW	
Any serious adverse events - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	very serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕◯◯◯ VERY LOW	

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: mean 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	very serious [a]	not serious	none	38	38	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕◯◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

Recommendation 3

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5); Upper respiratory symptoms (follow up: 8 weeks); Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial was identified comparing treatment with ivacaftor to placebo among persons 6 years or older with at least one non-gating mutation and baseline FEV1 greater than or equal to 40% (De Boeck et al., 2014).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a] [b]	**RR 0.80** (0.37 to 1.70)	Study population	
				297 per 1,000	**59 fewer per 1,000** (187 fewer to 208 more)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-		MD **12.82 higher** (11.81 higher to 13.83 higher)

Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
b. 95% CI includes line of no effect. Few events.

Additional considerations:

All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and

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		nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor. Long-term side effects of medications, cataracts, and other outcomes were not determined to be critical outcomes and thus not included in the evidence profile.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Research evidence:** Overall certainty of the evidence is based on the lowest certainty of the critical outcomes. **Additional considerations:** The panel was comfortable with rating down once for indirectness based on age and FEV1. In the De Boeck et al. 2014 study, the mean age reported was 22.8 years (range: 6-57). The age category of 6 to 11 year olds was not reported separately. The panel determined that FEV1 of 42% is not that indirect to 40%; however, the range extends beyond 90% (to 118%). Patients in the upper range (greater than 90%) may lead to a more conservative effect estimate. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that the balance between desirable and undesirable effects would favor treatment with ivacaftor.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc. **Additional considerations:** The panel agrees with the listed price.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The price of ivacaftor is in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. Additionally, the panel determine that the cost-effectiveness may favors the intervention because of downstream costs prevented (lung transplant, etc.); however, the cost-effectiveness may also favor the comparison based on the cost and sensitivity, if the modeled assumptions were altered to directly address this PICO. After two rounds of voting the panel decided that the cost-effectiveness varies. The panel would like this decision to be made by the practitioner to consider unique patient needs.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	**Research evidence:** No research evidence identified. **Additional considerations:**

	○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR modulator guideline panel suggests ivacaftor over no treatment for individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Low certainty in the evidence*				

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	Remarks -This is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with moderate to severe disease may be more likely to value potential improvement in these outcomes. The data available was not stratified by age and PPFEV1. While the PPFEV1 and age criteria of this group fall within the range of subjects recruited for this trial, the majority were older and a significant portion had PPFEV1 > 90% leading to indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more moderate to severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated, closed health systems.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions.

Evidence Profile for Recommendation 3

Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

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Recommendation 4

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized controlled trial was identified comparing treatment with ivacaftor to placebo among persons 6 years or older with at least one non-gating mutation and baseline FEV1 greater than or equal to 40% (De Boeck et al., 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation - Ivacaftor 150 mg BID
follow up: 8 weeks</td><td>75
(1 RCT)</td><td>⨁⨁◯◯
LOW[a] [b]</td><td>RR 0.80
(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>297 per 1,000</td><td>59 fewer per 1,000
(187 fewer to 208 more)</td></tr>
<tr><td>Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID</td><td>74
(1 RCT)</td><td>⨁⨁⨁◯
MODERATE[a]</td><td>-</td><td>The mean pulmonary function as measured by absolute change in percent predicted FEV1 -</td><td>MD 13.76 higher
(13.11 higher</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

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(MID: 6.5) Scale from: 0 to 90 follow up: 8 weeks				Ivacaftor 150 mg BID (MID: 6.5) was **0**	to 14.41 higher)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) was **0**	MD **12.82 higher** (11.81 higher to 13.83 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
b. 95% CI includes line of no effect. Few events.

Additional considerations:

Starting with healthier patients (>90%) may not have the magnitude of effects anticipated by the trial; however, the desirable effects are still large compared to other therapies used in CF. Patients with healthier lung functions have the greatest potential to maintain a health lung function.

All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer,

		serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel was comfortable with rating down once for indirectness based on age and FEV1. In the De Boeck et al. 2014 study, the mean age reported was 22.8 years (range: 6-57). The age category of 6 to 11 year olds was not reported separately. While the FEV1 level is broader in the studies than < 90% that is not expected to overestimate the effect. Imprecision was recognized for the outcomes of serious adverse events and pulmonary exacerbations. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel decided that the balance between desirable and undesirable effects would favor treatment with ivacaftor.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The price for ivacaftor is in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. Additionally, the panel determine that the cost-effectiveness may favors the intervention because of downstream costs prevented (lung transplant, etc.); however, the cost-effectiveness may also favor the comparison based on the cost and sensitivity, if the modeled assumptions were altered to directly address this PICO.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	**Research evidence:** No research evidence identified. **Additional considerations:**

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	○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR modulator guideline panel suggests ivacaftor over no treatment for individuals ages 6-11 and FEV1 greater than 90% with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Low certainty in the evidence* Remarks: -Even though expected absolute change might be small, patients might be more likely to maintain FEV1 predicted. -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations.				

	-Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease may place less value on potential improvement in these outcomes balanced against cost and potential side effects, though patients in this subgroup might benefit from a reduction in the rate of decline of their PPFEV1. The data within this study was not stratified by age and PPFEV1. While the PPFEV1 and age criteria of this group fall within the range of subjects recruited for this trial, the majority were older and had PPFEV1 < 90% which creates indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 4

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Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

Recommendation 5

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

ANNALSATS Articles in Press. Published on 17-January-2018 as 10.1513/AnnalsATS.201707-539OT

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients with CF mutation other than G551D or R117H with FEV1 less than 40%. One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (De Boeck 2014).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.80** (0.37 to 1.70)	Study population	
				297 per 1,000	**59 fewer per 1,000** (187 fewer to 208 more)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4)	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-		MD **12.82 higher** (11.81 higher to

Scale from: 0 to 100 follow up: 8 weeks					13.83 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

c. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
d. 95% CI includes line of no effect. Few events.

Additional consideration:

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		All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional consideration:** The panel was comfortable with rating down once for indirectness based on age and FEV1. The panel determined that FEV1 of 42% is not that indirect to 40%; however, the range extends beyond 90% (to 118%). Patients in the upper range (greater than 90%) may lead to a more conservative effect estimate. One concern of using this evidence to inform recommendations for persons at lower lung function is that treatment might not be able to fix impact on lung function and there may be more atypical disease course. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional consideration:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional consideration:** The panel decided that the balance between desirable and undesirable effects would probably favor treatment with ivacaftor.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc. **Additional considerations:** The panel agrees with the listed price.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional consideration:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. For persons with CF with non-gating mutations, the cost-effectiveness would favor the comparison.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	**Research evidence:** No research evidence identified. **Additional consideration:**

	○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional consideration:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability. The intervention would not be acceptable if the persons with CF have a non-gating mutation.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional consideration:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Low certainty in evidence*				

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	Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease might place less value on potential improvement in these outcomes balanced against cost and potential side effects. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. Patients with PPFEV1 < 40% were not included in the one RCT identified so that the evidence from that trial remains indirect in this subgroup. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more severe disease is present.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 5

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

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Recommendation 6

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3.5); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized trial was identified to address the research question (De Boeck 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation - Ivacaftor 150 mg BID
follow up: 8 weeks</td><td>75
(1 RCT)</td><td>⊕⊕◯◯
LOW[a b]</td><td>RR 0.80
(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>297 per 1,000</td><td>59 fewer per 1,000
(187 fewer to 208 more)</td></tr>
<tr><td>Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4)</td><td>74
(1 RCT)</td><td>⊕⊕⊕◯
MODERATE[a]</td><td>-</td><td></td><td>MD 12.82 higher
(11.81 higher to</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

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Scale from: 0 to 100 follow up: 8 weeks					13.83 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

e. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
f. 95% CI includes line of no effect. Few events.

Additional consideration:

		All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness for the age or FEV1 value. While the age range spans beyond 12-17 years, the estimate response is not expect to differ from the other age groups considered. The panel determined that FEV1 of 42% is not that indirect to 40%; however, the range extends beyond 90% (to 118%). Patients in the upper range (greater than 90%) may lead to a more conservative effect estimate. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel agreed that the balance of desirable effects probably outweighs undesirable effects when considering persons with CF with a gating mutation (e.g., G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5) and a cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. For persons with CF with non-gating mutations, the cost-effectiveness would favor the comparison.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015).

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	• Varies ○ Don't know	**Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability. The intervention would not be acceptable if the persons with CF have a non-gating mutation.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes • Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

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	JUDGEMENT							IMPLICATIONS
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Moderate certainty in evidence* Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient. (Two panel members were absent for discussion and vote on this recommendation)				
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy.				

	Patients with moderate to severe disease may be more likely to value potential improvement in these outcomes. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. The group mean for PPFEV1 was also contained within this subgroup reducing the degree of indirectness of the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in most situations where more moderate to severe disease is present.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 6

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

Recommendation 7

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3.5); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

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<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized trial was identified to address the research question (De Boeck 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation - Ivacaftor 150 mg BID
follow up: 8 weeks</td><td>75
(1 RCT)</td><td>⨁⨁◯◯
LOW[a] [b]</td><td>RR 0.80
(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>297 per 1,000</td><td>59 fewer per 1,000
(187 fewer to 208 more)</td></tr>
<tr><td>Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4)</td><td>74
(1 RCT)</td><td>⨁⨁⨁◯
MODERATE[a]</td><td>-</td><td></td><td>MD 12.82 higher
(11.81 higher</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

Scale from: 0 to 100 follow up: 8 weeks					to 13.83 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

g. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
h. 95% CI includes line of no effect. Few events.

Additional consideration:

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		Starting with healthier patients (>90%) may not have the magnitude of effects anticipated by the trial; however, the desirable effects are still large compared to other therapies used in CF. Patients with healthier lung functions have the greatest potential to maintain a health lung function. All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness for the age or FEV1 value. While the age range spans beyond 12-17 years, the estimate response is not expect to differ from the other age groups considered. Additionally, while the FEV1 level is broader in the studies than < 90% that is not expected to overestimate the effect. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel agreed that the balance of desirable effects probably outweighs undesirable effects when considering persons with CF with a gating mutation (e.g., G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. For persons with CF with non-gating mutations, the cost-effectiveness would favor the comparison.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	**Research evidence:** No research evidence identified. **Additional considerations:**

	○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability. The intervention would not be acceptable if the persons with CF have a non-gating mutation.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor over no treatment for individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Moderate certainty in evidence* Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations.				

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	-Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease may place less value on potential improvement in these outcomes balanced against cost and potential side effects. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. While there was no upper bound in PPFEV1 the majority of subjects had a PPFEV1 < 90% which creates indirectness in the evidence. The overall consensus of the group was that patients, parents, and providers would be likely to use this medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 7

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

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Recommendation 8

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients with CF mutation other than G551D or R117H with FEV1 less than 40%. One randomized trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (De Boeck 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation - Ivacaftor 150 mg BID
follow up: 8 weeks</td><td>75
(1 RCT)</td><td>⨁⨁◯◯
LOW[a b]</td><td>RR 0.80
(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>297 per 1,000</td><td>59 fewer per 1,000
(187 fewer to 208 more)</td></tr>
<tr><td>Quality of life as measured by CFQ-R respiratory domain</td><td>74
(1 RCT)</td><td>⨁⨁⨁◯
MODERATE[a]</td><td>-</td><td></td><td>MD 12.82 higher
(11.81 higher</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

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	score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 8 weeks					to 13.83 higher)
	Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
	Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
					184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
	Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
					189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
	Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

i. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
j. 95% CI includes line of no effect. Few events.

		Additional consideration: All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness for the age. While the age range spans beyond 18+ years, the estimate response is not expect to differ from the other age groups considered. The panel agreed to rate down once for indirectness based FEV1 value. The panel determined that FEV1 of 42% is not that indirect to 40%; however, the range extends beyond 90% (to 118%). Patients in the upper range (greater than 90%) may lead to a more conservative effect estimate. One concern of using this evidence to inform recommendations for persons at lower lung function is that treatment might not be able to fix impact on lung function and there may be more atypical disease course. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel agreed that the balance of desirable effects probably outweighs undesirable effects when considering persons with CF with a gating mutation (e.g., G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. For persons with CF with non-gating mutations, the cost-effectiveness would favor the comparison.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	**Research evidence:** No research evidence identified. **Additional considerations:**

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	○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability. The intervention would not be acceptable if the persons with CF have a non-gating mutation.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Low certainty in evidence*				

	Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with less severe disease might place less value on potential improvement in these outcomes balanced against cost and potential side effects. The data available were not stratified by age and PPFEV1 status but the ages included in this include the group mean. Patients with PPFEV1 < 40% were not included in the one RCT identified so that the evidence from that trial remains indirect in this subgroup. The overall consensus of the group was that patients, and providers would be likely to use this medication in most situations where more severe disease is present.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 8

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

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1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⨁⨁◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⨁⨁◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

Recommendation 9

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID ; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

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<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (De Boeck 2014).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
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(0.37 to 1.70)</td><td colspan="2">Study population</td></tr>
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(11.81 higher</td></tr>
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<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

(MID: 4) Scale from: 0 to 100 follow up: 8 weeks					to 13.83 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

k. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
l. 95% CI includes line of no effect. Few events.

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		Additional consideration: All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness for the age or FEV1 value. While the age range spans beyond 18+ years, the estimate response is not expect to differ from the other age groups considered. The panel determined that FEV1 of 42% is not that indirect to 40%; however, the range extends beyond 90% (to 118%). Patients in the upper range (greater than 90%) may lead to a more conservative effect estimate. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel agreed that the balance of desirable effects probably outweighs undesirable effects when considering persons with CF with a gating mutation (e.g., G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services. For persons with CF with non-gating mutations, the cost-effectiveness would favor the comparison.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact	**Research evidence:** No research evidence identified. **Additional considerations:**

	○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability. The intervention would not be acceptable if the persons with CF have a non-gating mutation.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Moderate certainty in evidence*				

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	Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with more moderate to severe disease may be more likely to value potential improvement in these outcomes. The data available were not stratified by age and PPFEV1 status but the age range of this subgroup included the group mean. The group mean for PPFEV1 was also contained within this subgroup, reducing the degree of indirectness of the evidence. The overall consensus of the group was that patients and providers would be likely to use this medication in most situations where more moderate to severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 9

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

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Recommendation 10

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H**?

POPULATION:	individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was initially used to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation): G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. *In vitro* research suggests that IVA would potentiate chloride transport and improve clinical outcomes in a genetically diverse group of patients with CF who carry one of these non-G551D gating mutations.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3); Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
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<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. The G551D genotype is the third most common mutation in the US accounting for approximately 4% of the CF population. Non-G551D gating mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D account for approximately 1% of the CF population, but as they would expect to have a similar response to ivacaftor therapy as patients with a G551D mutation, individuals with CF with these mutations are an important group to consider.

Additional considerations:

This question only refers to persons with CF and non-G551D gating mutations. This question does not consider persons with CF with non-gating mutations.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest (De Boeck 2014).

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<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
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MODERATE[a]</td><td>-</td><td></td><td>MD 12.82 higher
(11.81 higher</td></tr>
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<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
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mg BID (MID: 4) Scale from: 0 to 100 follow up: 8 weeks					to 13.83 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 8 weeks	74 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **13.76 higher** (13.11 higher to 14.41 higher)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 8 weeks	76 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.86** (0.32 to 2.31)	Study population	
				184 per 1,000	**26 fewer per 1,000** (125 fewer to 241 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 8 weeks	75 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.56** (0.18 to 1.74)	Study population	
				189 per 1,000	**83 fewer per 1,000** (155 fewer to 140 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 8 weeks	75 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.66 higher** (0.44 higher to 0.88 higher)

m. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).
n. 95% CI includes line of no effect. Few events.

		Additional consideration: Starting with healthier patients (>90%) may not have the magnitude of effects anticipated by the trial; however, the desirable effects are still large compared to other therapies used in CF. Patients with healthier lung functions have the greatest potential to maintain a health lung function. All outcomes suggest desirable effects. Pulmonary exacerbations are reduced, improvement in QoL of 12 points (this is larger than the clinically important difference identified in the literature of 4 points), pulmonary function improves from baseline to end of study, minimally important difference (6.5), respiratory symptoms are fewer, serious adverse events are fewer for the intervention group, and nutritional status (measured by BMI is .66 higher (this is larger than the minimally important difference identified in the literature of .3). Some patients did have increased adverse events reported at start of treatment. Dehydration, convulsion, dizziness, DIOS were experienced by patients receiving treatment; however, the patients' histories are unknown adding uncertainty to whether or not these events were related to the treatment. Undesirable effects judgment was based on the worst case scenario that all three serious adverse events occurred because of treatment with ivacaftor.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional evidence:** The panel decided to not rate down for indirectness for the age or FEV1 value. While the age range spans beyond 18+ years, the estimate response is not expect to differ from the other age groups considered. Additionally, while the FEV1 level is broader in the studies than > 90% that is not expected to overestimate the effect. Imprecision was recognized for the outcomes of pulmonary exacerbations, lower respiratory events, and serious adverse events. The panel also discussed some uncertainty because the study reported on results at eight weeks.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Research evidence:** No research evidence identified. **Additional evidence:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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	○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional evidence:** The panel agreed that the balance of desirable effects probably outweighs undesirable effects when considering persons with CF with a gating mutation (e.g., G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D).
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional evidence:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. The panel recognizes that persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence available. **Additional evidence:**

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	● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional evidence:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence available. **Additional evidence:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor over no treatment for individuals age 18 years and older and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H. *Conditional recommendation, Moderate certainty in the evidence* Remarks: -This recommendation is specific to persons with CF with G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D mutations. -Decisions on whether or not to prescribe ivacaftor may vary based on insurance coverage and cost to the patient.				

JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Patients with more severe disease may be more likely to value potential improvement in these outcomes. The data available were not stratified by age and PPFEV1 status but the ages included in this subgroup were closer to the group mean. While there was no upper bound in PPFEV1 the majority of subjects had a PPFEV1 < 90% which retains some degree of indirectness in the evidence. The overall consensus of the group was that patients and providers would be likely to use this medication in many situations but other factors would also be considered where less severe disease is present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.
SUBGROUP CONSIDERATIONS	This recommendation is developed for persons with CF who have the following mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D. This is because the trial specifically evaluated the effect of treatment among persons with CF who have gating mutations. In vitro studies were not considered to inform this recommendation.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 10

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with mutations other than G551D and R117H

Setting: Outpatient

Bibliography: De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis, 13(6), 674-680.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	9/38 (23.7%)	11/37 (29.7%)	**RR 0.80** (0.37 to 1.70)	**59 fewer per 1,000** (from 187 fewer to 208 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **12.82 higher** (11.81 higher to 13.83 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 8 weeks; Scale from: 0 to 90)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	37	37	-	MD **13.76 higher** (13.11 higher to 14.41 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	6/38 (15.8%)	7/38 (18.4%)	**RR 0.86** (0.32 to 2.31)	**26 fewer per 1,000** (from 125 fewer to 241 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [b]	none	4/38 (10.5%)	7/37 (18.9%)	**RR 0.56** (0.18 to 1.74)	**83 fewer per 1,000** (from 140 more to 155 fewer)	⊕⊕◯◯ LOW	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 8 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	38	37	-	MD **0.66 higher** (0.44 higher to 0.88 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Study population characteristics: age = 22.8 years (6-57); FEV1 = 78.4% (42.9-118.7).

b. 95% CI includes line of no effect. Few events.

Recommendation 11

Should **ivacaftor** vs. **no treatment** be used for **individuals age 0-5 years with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 0-5 years with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Any pulmonary exacerbation - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients aged 0 to 5 years with CF mutation R117H. One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest 6 years and older (Moss 2015).

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	17 (1 RCT)	⊕⊕◯◯ LOW[a] [b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **6.3 lower** (8.07 lower to 4.53 lower)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID	17 (1 RCT)	⊕⊕◯◯ LOW[a] [b]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID was **0**	MD **6.1 lower** (9.01 lower to 3.19 lower)

Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a] [b c d]	**RR 0.87** (0.45 to 1.67)	Study population		
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)	
Any serious adverse event - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a] [b d e]	**RR 4.50** (0.25 to 81.76)	Study population		
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	
Upper respiratory symptoms - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a] [b d e]	**RR 0.36** (0.09 to 1.35)	Study population		
				625 per 1,000	**400 fewer per 1,000** (569 fewer to 219 more)	
Lower respiratory symptoms - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a] [b d e]	**RR 0.89** (0.07 to 12.00)	Study population		
				125 per 1,000	**14 fewer per 1,000** (116 fewer to 1,375 more)	
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a] [b d]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.18 lower** (0.92 lower to 0.56 higher)	

a. All patients FEV1 reported ≥70%.
b. All patients ages 6 years and older.
c. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

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		d. 95% CI crosses line of no effect. e. Few events. **Additional considerations:** The evidence is based on one study. Exacerbations improved but imprecise. No other improvements. Sweat chloride improved, although not determined by the panel to be a critical outcome. QoL is reduced. Adverse events no change between groups.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel recognized a lot of uncertainty in the estimates of effects because of very serious indirectness due to age and FEV1 level. While the most appropriate age group to inform these recommendations from would be the 6-11 age group, it is still very indirect. Dosage recommendations available for pediatric population (2-6 years). Conditional against for 6-11 greater than 90%.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5) and a cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	**Research evidence:** No research evidence identified. **Additional considerations:**

	○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 0-5 years with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○
RECOMMENDATION	The CFTR guideline panel suggests against ivacaftor vs. no treatment be used in individuals age 0-5 years with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence*				

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	Remarks: -Based on the indirectness of the evidence, the panel prioritized any possible harm from the treatment over unknown or no known benefit of the treatment -Many patients/families/clinicians may not want to provide this medication in individuals age 0-5 with normal lung function/few symptoms (if lung function cannot be measured) because of uncertainty in harms and long-term consequences. -No dosing information on 0-2 years and on-going infant trial does not include R117H
JUSTIFICATION	This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The overall consensus of the group was that parents and providers would be unlikely to use this medication in children with few symptoms and minimal disease. However, given the high variability of disease severity, providers and families may still consider the use of this medication where more severe disease, more rapidly progressive disease, or more frequent exacerbations are present. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated, closed health systems. During the panel meeting, the panel decided to vote twice on these recommendations to decide whether to address them in the current recommendations or refer readers to the previously published consensus guidelines on preschoolers. Proposed - conditional against - no benefit and possible harm. Vote: Use preschool guidelines - 8 Address in these guidelines - 3 Could address in the introduction that it's been addressed in other guidelines. Preschool does not address infants. No formulation for those under 2 years. "For children with CF 2-5, preschool guideline recommends routine use of ivacaftor with gating mutations and consideration for R117H mutation. Vote 2: Address in these guidelines - 9 Use preschool - 2

	Look at open label studies and bring back to the panel. Will research and bring back to the group for a discussion. No new data since pre-school guidelines released. Evidence of harm in older age groups. Discussion from second meeting regarding the 0-5 age group questions: Preschool guidelines recommend ivacaftor but did not consider Moss study (published prior to Moss) KIWI study does not include R117H (n=1) New evidence available since the preschool guidelines (Moss). FDA approved for 2 years and above for specific mutations. Consider that this age group has higher lung function? But not in patients among patients with R117H. Clinicians will have the ability to make their decision based on the information in this recommendation. Vote: Agree: 9 Disagree: 0 Absent: 3
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.

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RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

Evidence Profile for Recommendation 11

Ivacaftor compared to no treatment in individuals age 0-5 years with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	not serious	none	9	8	-	MD **6.3 lower** (8.07 lower to 4.53 lower)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	not serious	none	9	8	-	MD **6.1 lower** (9.01 lower to 3.19 lower)	⊕⊕◯◯ LOW	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b,c]	serious [d]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [a,b]	very serious [d,e]	none	2/9 (22.2%)	0/8 (0.0%)	**RR 4.50** (0.25 to 81.76)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	very serious [d,e]	none	2/9 (22.2%)	5/8 (62.5%)	**RR 0.36** (0.09 to 1.35)	**400 fewer per 1,000** (from 219 more to 569 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Lower respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	very serious [d,e]	none	1/9 (11.1%)	1/8 (12.5%)	**RR 0.89** (0.07 to 12.00)	**14 fewer per 1,000** (from 116 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [d]	none	9	8	-	MD **0.18 lower** (0.92 lower to 0.56 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. All patients FEV1 reported ≥70%.

b. All patients ages 6 years and older.

c. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

d. 95% CI crosses line of no effect.

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e. Few events.

Recommendation 12

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
● Small
○ Moderate
○ Large

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients with CF mutation R117H with FEV1 less than 40%. One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (Moss 2015).

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Quality of life as measured by CFQ-R respiratory domain	17 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life as measured by CFQ-R respiratory domain	MD **6.1 lower** (9.01 lower

score - Ivacaftor 150 mg BID				score - Ivacaftor 150 mg BID was **0**	to 3.19 lower)
Upper respiratory symptoms - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a c d]	**RR 0.36** (0.09 to 1.35)	Study population	
				625 per 1,000	**400 fewer per 1,000** (569 fewer to 219 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a c d]	**RR 0.89** (0.07 to 12.00)	Study population	
				125 per 1,000	**14 fewer per 1,000** (116 fewer to 1,375 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	17 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **6.3 lower** (8.07 lower to 4.53 lower)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	17 (1 RCT)	⊕⊕◯◯ LOW[a c]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.18 lower** (0.92 lower to 0.56 higher)
Any serious adverse event - Ivacaftor 150 mg BID	17 (1 RCT)	⊕◯◯◯ VERY LOW[a c d]	**RR 4.50** (0.25 to 81.76)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

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		a. All patients FEV1 reported ≥70%. b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. c. 95% CI crosses line of no effect. d. Few events. **Additional considerations:** Both group mean and subgroup mean of interest were examined. The panel had difficulty extrapolating from 6-11 with a mean of FEV1 90%. When looking at the study group aggregate mean, the absolute change in percent predicted is 2.1%, which would be proportionally beneficial with a lower FEV1 level, such as below 40%.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** FEV1 from Moss only includes 70% and greater for 6-11 year age group and the aggregate study data is more indirect to this age group.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** For this group, even a small benefit would be of value to the patient. The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel has some uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5) and a cost of 182,000 pounds/year for ivacaftor. Considerations: Difference in FEV1 predicted between persons in De Boeck (13.76; 95% CI: 13.11; 14.41). **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	**Research evidence:** No research evidence identified. **Additional considerations:**

	○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence*				

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	Remarks: - Recognizing the uncertainty in the evidence, treatment with ivacaftor may be preferred by persons who are of low FEV1 level or are declining on usual case, but typically adherent to treatment.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although, the balance between these values will vary widely among patients with R117H, patients in this age range with severe disease already present likely represent individuals for whom treatment would be favored. The data available did stratify by age and PPFEV1 status but the strata representing individuals aged 6-11 years contained very few individuals with compromised lung function, providing less likelihood of substantial improvement from baseline as well as possible over-representation of individuals with limited disease penetrance. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 12

Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.1 lower** (9.01 lower to 3.19 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	5/8 (62.5%)	**RR 0.36** (0.09 to 1.35)	**400 fewer per 1,000** (from 219 more to 569 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	1/9 (11.1%)	1/8 (12.5%)	**RR 0.89** (0.07 to 12.00)	**14 fewer per 1,000** (from 116 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.3 lower** (8.07 lower to 4.53 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [a]	serious [c]	none	9	8	-	MD **0.18 lower** (0.92 lower to 0.56 higher)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	0/8 (0.0%)	**RR 4.50** (0.25 to 81.76)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. All patients FEV1 reported ≥70%.

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b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

c. 95% CI crosses line of no effect.

d. Few events.

Recommendation 13

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5); Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H (Moss 2015).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID follow up: 24 weeks	69 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	17 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) was **0**	MD **6.1 lower** (9.01 lower to 3.19 lower)

Upper respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 0.36** (0.09 to 1.35)	Study population	
				625 per 1,000	**400 fewer per 1,000** (569 fewer to 219 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 0.89** (0.07 to 12.00)	Study population	
				125 per 1,000	**14 fewer per 1,000** (116 fewer to 1,375 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 150 follow up: 24 weeks	17 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **6.3 lower** (8.07 lower to 4.53 lower)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 24 weeks	17 (1 RCT)	⊕⊕◯◯ LOW[a b]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.18 lower** (0.92 lower to 0.56 higher)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 4.50** (0.25 to 81.76)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. 95% CI crosses line of no effect.

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		b. All patients FEV1 reported ≥70%. c. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. d. Few events. **Additional considerations:** The evidence is based on one study. Exacerbations improved but imprecise. No other improvements. Sweat chloride improved, although not determined by the panel to be a critical outcome. The panel decided on trivial for the effect of the desirable outcomes. The panel determined that there is possibly small undesirable effects.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel recognized a lot of uncertainty in the estimates of effects.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

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	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

	JUDGEMENT							IMPLICATIONS
			the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR guideline panel suggests ivacaftor over no treatment for individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence* Remarks:				

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	-For the following conditions, the panel would not favor treatment with ivacaftor: -Asymptomatic or relatively asymptomatic patients with normal lung function; -Persons who have been shown to be not adherent to treatment; -Unknown/uncertain long-term benefits/consequences; -Some persons with low FEV1 might respond to the treatment; -Someone declining on usual care who is adherent to treatment.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H and likely reflect relative lung function. The data available did stratify by age and PPFEV1 status but the strata representing individuals aged 6-11 contained very few individuals with compromised lung function providing less likelihood of substantial improvement from baseline as well as possible over-representation of individuals with limited disease penetrance. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care. The panel voted twice to develop the recommendations based on limited certainty in the evidence and variability between persons with CF with the R117H mutation and different poly T genotypes. The results of the votes are as follows: Panel vote 1: Cond for ivacaftor: 4 Cond against ivacaftor: 2 Return to the evidence and examine the aggregate data: 5 The panel decided to examine the aggregate data from Moss. If looking at aggregate Moss, there are significant improvements in QoL. However, the panel was concerned that persons 11 years and older might be too indirect to inform recommendation. The panel voted a second time: Panel vote 2:

	Cond for ivacaftor: 9 Cond against ivacaftor: 2 The majority of the panel voted for conditional for ivacaftor instead of against, so that when appropriate, this treatment would be available to prescribe. When considering this treatment for persons with CF with the R117H mutation, clinicians should consider these remarks: -For the following conditions, the panel would not favor treatment with ivacaftor: -Asymptomatic or relatively asymptomatic patients with normal lung function; -Persons who have been shown to be not adherent to treatment; -Unknown/uncertain long-term benefits/consequences; -Some persons with low FEV1 might respond to the treatment; -Someone declining on usual care who is adherent to treatment.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 13

Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.1 lower** (9.01 lower to 3.19 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	5/8 (62.5%)	**RR 0.36** (0.09 to 1.35)	**400 fewer per 1,000** (from 219 more to 569 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	1/9 (11.1%)	1/8 (12.5%)	**RR 0.89** (0.07 to 12.00)	**14 fewer per 1,000** (from 116 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 24 weeks; Scale from: 0 to 150)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.3 lower** (8.07 lower to 4.53 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	serious [c]	none	9	8	-	MD **0.18 lower** (0.92 lower to 0.56 higher)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	0/8 (0.0%)	**RR 4.50** (0.25 to 81.76)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. All patients FEV1 reported ≥70%.

b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

c. 95% CI crosses line of no effect.

d. Few events

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Recommendation 14

Should **ivacaftor** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5); Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?

● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H (Moss 2015).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Any pulmonary exacerbation - Ivacaftor 150 mg BID
follow up: 24 weeks</td><td>69
(1 RCT)</td><td>⨁⨁◯◯
LOW[a b c]</td><td>RR 0.87
(0.45 to 1.67)</td><td colspan="2">Study population</td></tr>
<tr><td></td><td></td><td></td><td></td><td>371 per 1,000</td><td>48 fewer per 1,000
(204 fewer to 249 more)</td></tr>
<tr><td>Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4)</td><td>17
(1 RCT)</td><td>⨁⨁⨁◯
MODERATE[b]</td><td>-</td><td>The mean quality of life as measured by CFQ-R respiratory domain</td><td>MD 6.1 lower
(9.01 lower</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td></tr>
</table>

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Scale from: 0 to 100 follow up: 24 weeks				score - Ivacaftor 150 mg BID (MID: 4) was **0**	to 3.19 lower)
Upper respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 0.36** (0.09 to 1.35)	Study population	
				625 per 1,000	**400 fewer per 1,000** (569 fewer to 219 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 0.89** (0.07 to 12.00)	Study population	
				125 per 1,000	**14 fewer per 1,000** (116 fewer to 1,375 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) Scale from: 0 to 90 follow up: 24 weeks	17 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) was **0**	MD **6.3 lower** (8.07 lower to 4.53 lower)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) Scale from: 12 to 22 follow up: 24 weeks	17 (1 RCT)	⊕⊕◯◯ LOW[a b]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.18 lower** (0.92 lower to 0.56 higher)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 24 weeks	17 (1 RCT)	⊕◯◯◯ VERY LOW[a b d]	**RR 4.50** (0.25 to 81.76)	Study population	
				0 per 1,000	**0 fewer per 1,000**

		<table><tr><td></td><td></td><td></td><td></td><td></td><td>(0 fewer to 0 fewer)</td></tr></table> a. 95% CI crosses line of no effect. b. All patients FEV1 reported ≥70%. c. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. d. Few events. **Additional considerations:** The evidence is based on one study. Exacerbations improved but imprecise. No other improvements. Sweat chloride improved, although not determined by the panel to be a critical outcome. The panel decided on trivial for the effect of the desirable outcomes. The panel determined that there is possibly small undesirable effects.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness based on FEV1 level.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	**Research evidence:** No research evidence identified. **Additional considerations:** More uncertain about the value of the outcomes as the treatment would have the potential to lower QoL and FEV1 level.

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	○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
			the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○
RECOMMENDATION	The CFTR suggests against ivacaftor vs no treatment for individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Low certainty in the evidence* Remarks:				

	-Many patients/families/clinicians may not want to provide this medication in individuals age 6-11 with normal lung function because of uncertainty in harms and long-term consequences.
JUSTIFICATION	This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The available data stratified by age and PPFEV1 status were more closely matched within this subgroup than for those with more severely reduced lung function. The overall consensus of the group was that patients, parents, and providers would be much less likely to use this medication in this situation, but that providers and families may still consider the use of this medication where more rapidly progressive disease is present, there are frequent exacerbations, or patients have lower baseline lung function. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profiles for Recommendation 14

Ivacaftor compared to no treatment in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.1 lower** (9.01 lower to 3.19 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	5/8 (62.5%)	**RR 0.36** (0.09 to 1.35)	**400 fewer per 1,000** (from 219 more to 569 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	1/9 (11.1%)	1/8 (12.5%)	**RR 0.89** (0.07 to 12.00)	**14 fewer per 1,000** (from 116 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 6.5) (follow up: 24 weeks; Scale from: 0 to 90)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	not serious	none	9	8	-	MD **6.3 lower** (8.07 lower to 4.53 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 22)												
1	randomized trials	not serious	not serious	serious [a]	serious [c]	none	9	8	-	MD **0.18 lower** (0.92 lower to 0.56 higher)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	very serious [c,d]	none	2/9 (22.2%)	0/8 (0.0%)	**RR 4.50** (0.25 to 81.76)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. All patients FEV1 reported ≥70%.

b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

c. 95% CI crosses line of no effect.

d. Few events

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Recommendation 15

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
● Small
○ Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H; however, only two participants were between the ages of 12 and 17 years and not included in the analysis (Moss 2015).

Therefore the aggregate data from Moss et al. was used to inform the evidence.

Outcomes	**№ of participants (studies) Follow up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with no treatment	**Risk difference with ivacaftor**
Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Quality of life as measured by CFQ-R respiratory domain	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain	MD **8.4 higher** (7.36 higher

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score - Ivacaftor 150 mg BID				score - Ivacaftor 150 mg BID was **0**	to 9.44 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **2.1 higher** (1.56 higher to 2.64 higher)
Upper respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 5.15** (0.63 to 41.80)	Study population	
				29 per 1,000	**119 more per 1,000** (11 fewer to 1,166 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 1.40** (0.84 to 2.31)	Study population	
				400 per 1,000	**160 more per 1,000** (64 fewer to 524 more)
Any serious adverse event - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 0.69** (0.21 to 2.22)	Study population	
				171 per 1,000	**53 fewer per 1,000** (135 fewer to 209 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.26 higher** (0.05 lower to 0.57 higher)

		a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. b. Only two patients were of 12-17 years, this is aggregate data from all age group. c. 95% CI crosses line of no effect. **Additional considerations:** Statistically and clinically improvement in QoL. The panel determined that there is possibly small undesirable effects. These include cataracts, liver function, and interference with oral contraceptives.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** Since only two patients fell into the 12-17 year age group, the panel decided to use the aggregate data to inform this question. If not using the group mean, then not including the two persons 12-17 years.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The aggregate evidence is in favor of the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
			the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence* Remarks:				

	-More patients/clinicians might be willing to use because of the more severe disease progression -Persons in this age group are likely to be the least adherent
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although, the balance between these values will vary widely among patients with R117H, patients in this age range with severe disease already present likely represent individuals for whom treatment would be favored. The data available did stratify by age and PPFEV1 status but the stratum representing individuals aged 12-17 years contained only two individuals. The overall consensus of the group was that most patients, parents, and providers would be likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 15

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **8.4 higher** (7.36 higher to 9.44 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **2.1 higher** (1.56 higher to 2.64 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	5/34 (14.7%)	1/35 (2.9%)	**RR 5.15** (0.63 to 41.80)	**119 more per 1,000** (from 11 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	19/34 (55.9%)	14/35 (40.0%)	**RR 1.40** (0.84 to 2.31)	**160 more per 1,000** (from 64 fewer to 524 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	4/34 (11.8%)	6/35 (17.1%)	**RR 0.69** (0.21 to 2.22)	**53 fewer per 1,000** (from 135 fewer to 209 more)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **0.26 higher** (0.05 lower to 0.57 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

b. Only two patients were of 12-17 years, this is aggregate data from all age group.

c. 95% CI crosses line of no effect.

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Recommendation 16

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
● Small
○ Moderate
○ Large

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H; however, only two participants were between the ages of 12 and 17 years and not included in the analysis (Moss 2015).

Therefore the aggregate data from Moss et al. was used to inform the evidence.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain score	MD **8.4 higher** (7.36 higher

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				- Ivacaftor 150 mg BID was **0**	to 9.44 higher)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **2.1 higher** (1.56 higher to 2.64 higher)
Upper respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 5.15** (0.63 to 41.80)	Study population	
				29 per 1,000	**119 more per 1,000** (11 fewer to 1,166 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 1.40** (0.84 to 2.31)	Study population	
				400 per 1,000	**160 more per 1,000** (64 fewer to 524 more)
Any serious adverse event - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 0.69** (0.21 to 2.22)	Study population	
				171 per 1,000	**53 fewer per 1,000** (135 fewer to 209 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.26 higher** (0.05 lower to 0.57 higher)

		a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. b. Only two patients were of 12-17 years, this is aggregate data from all age group. c. 95% CI crosses line of no effect. **Additional considerations:** Statistically and clinically improvement in QoL. The panel determined that there is possibly small undesirable effects. These include cataracts, liver function, and interference with oral contraceptives.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** Since only two patients fell into the 12-17 year age group, the panel decided to use the aggregate data to inform this question. If not using the group mean, then not including the two persons 12-17 years.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The aggregate evidence is in favor of the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
			the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	CFTR suggest ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence* Remarks,				

	-More patients/clinicians might be willing to use because of more severe disease progression -Persons in this age group are likely to be the least adherent
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H and likely reflect relative lung function. The data available did stratify by age and PPFEV1 status but the strata representing individuals aged 12-17 years contained only two individuals. The overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while adherent to usual care.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 16

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **8.4 higher** (7.36 higher to 9.44 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **2.1 higher** (1.56 higher to 2.64 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	5/34 (14.7%)	1/35 (2.9%)	**RR 5.15** (0.63 to 41.80)	**119 more per 1,000** (from 11 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	19/34 (55.9%)	14/35 (40.0%)	**RR 1.40** (0.84 to 2.31)	**160 more per 1,000** (from 64 fewer to 524 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	4/34 (11.8%)	6/35 (17.1%)	**RR 0.69** (0.21 to 2.22)	**53 fewer per 1,000** (from 135 fewer to 209 more)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	34	35	-	MD **0.26 higher** (0.05 lower to 0.57 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

b. Only two patients were of 12-17 years, this is aggregate data from all age group.

c. 95% CI crosses line of no effect.

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Recommendation 17

Should **ivacaftor** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
● Small
○ Moderate
○ Large

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H; however, only two participants were between the ages of 12 and 17 years and not included in the analysis (Moss 2015).

Therefore the aggregate data from Moss et al. was used to inform the evidence.

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Quality of life as measured by CFQ-R respiratory domain	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain	MD **8.4 higher** (7.36 higher

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score - Ivacaftor 150 mg BID				score - Ivacaftor 150 mg BID was **0**	to 9.44 higher)
Upper respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 5.15** (0.63 to 41.80)	Study population	
				29 per 1,000	**119 more per 1,000** (11 fewer to 1,166 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 1.40** (0.84 to 2.31)	Study population	
				400 per 1,000	**160 more per 1,000** (64 fewer to 524 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **2.1 higher** (1.56 higher to 2.64 higher)
Any serious adverse event - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 0.69** (0.21 to 2.22)	Study population	
				171 per 1,000	**53 fewer per 1,000** (135 fewer to 209 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	69 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.26 higher** (0.05 lower to 0.57 higher)

		a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. b. Only two patients were of 12-17 years, this is aggregate data from all age group. c. 95% CI crosses line of no effect. **Additional considerations:** Statistically and clinically improvement in QoL. The panel determined that there is possibly small undesirable effects. These include cataracts, liver function, and interference with oral contraceptives.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** Since only two patients fell into the 12-17 year age group, the panel decided to use the aggregate data to inform this question. If not using the group mean, then not including the two persons 12-17 years.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The aggregate evidence is in favor of the intervention.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies.

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		While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

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Should ivacaftor vs. no treatment be used in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The CFTR suggests against ivacaftor vs no treatment for individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty* Remarks: -Many patients/families/clinicians may not want to provide this medication in 12-17 with normal lung function because of uncertainty in harms and long-term consequences. -Patients who are more symptomatic, declining on usual care, lower FEV1 (closer to 90%) may prefer treatment with ivacaftor.				
JUSTIFICATION	This recommendation places a high value on the substantial expected costs of the therapy and potential side effects of therapy as well as the lack of improvement of patient-important outcomes such as lung function as assessed by PPFEV1. The data available, stratified by PPFEV1 status, were more closely matched within this subgroup that for those with more severely reduced lung function. The overall consensus of the group was that patients and providers would be much less likely to use this medication in this situation but that providers, parents, and families may still consider the use of this medication where more rapidly progressive disease is present or frequent exacerbation are present or patients with an PPFEV1 at the lower end of this range (closer to 90%). The high cost of the medication may also limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems.				
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the				

	uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 17

Ivacaftor compared to no treatment in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **8.4 higher** (7.36 higher to 9.44 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	5/34 (14.7%)	1/35 (2.9%)	**RR 5.15** (0.63 to 41.80)	**119 more per 1,000** (from 11 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	19/34 (55.9%)	14/35 (40.0%)	**RR 1.40** (0.84 to 2.31)	**160 more per 1,000** (from 64 fewer to 524 more)	⊕⊕◯◯ LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **2.1 higher** (1.56 higher to 2.64 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	4/34 (11.8%)	6/35 (17.1%)	**RR 0.69** (0.21 to 2.22)	**53 fewer per 1,000** (from 135 fewer to 209 more)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	34	35	-	MD **0.26 higher** (0.05 lower to 0.57 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

b. Only two patients were of 12-17 years, this is aggregate data from all age group.

c. 95% CI crosses line of no effect.

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Recommendation 18

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID; Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Respiratory symptoms - cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID; Glycemic control as measured by blood glucose level - Ivacaftor 150 mg BID; Microbiological profile as measured by incidence of pseudomonas - Ivacaftor 150 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - Ivacaftor 150 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials addressed whether ivacaftor or no treatment should be used among patients with CF mutation R117H with FEV1 less than 40%. One randomized controlled trial reported on ivacaftor vs no treatment among the population of interest with FEV1 greater than 40% (Moss 2015).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID	69 (1 RCT)	⊕◯◯◯ VERY LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID was **0**	MD **5 higher** (4.25 higher to 5.75 higher)

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

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Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID was **0**	MD **12.7 higher** (11.23 higher to 14.17 higher)
Upper respiratory symptoms - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕◯◯ LOW[b c d]	**RR 2.71** (0.98 to 7.50)	Study population	
				154 per 1,000	**263 more per 1,000** (3 fewer to 1,000 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 1.08** (0.77 to 1.53)	Study population	
				692 per 1,000	**55 more per 1,000** (159 fewer to 367 more)
Any serious adverse event - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕◯◯ LOW[b c d]	**RR 0.36** (0.08 to 1.62)	Study population	
				231 per 1,000	**148 fewer per 1,000** (212 fewer to 143 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕◯◯ LOW[b c]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID was **0**	MD **0.31 higher** (0.13 lower to 0.75 higher)

Additional considerations:

		The evidence is based on one study. Exacerbations improved but imprecise. No other improvements. Sweat chloride improved, although not determined by the panel to be a critical outcome. The absolute change in percent predicted is 2.1%, which would be proportionally beneficial with a lower FEV1 level, such as below 40%. The panel determined that there is possibly small undesirable effects.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel decides to rate down to very serious for indirectness based on FEV1 level.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered and that for this group, even a small benefit would be of value to the patient. The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel has some uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR guideline panel suggests ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Very low certainty in the evidence*				

	Remarks: -Persons with FEV1 levels of less than 40% predicted might show benefit; however, less certainty in the directness of the data
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H due to the high variability of clinical outcomes in individuals with this mutation, but patients with severe disease already present would represent those for whom treatment would be favored. The data was stratified for this age group. The overall consensus of the group was that patients and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 18

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn, JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	very serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	24	26	-	MD **5 higher** (4.25 higher to 5.75 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	24	26	-	MD **12.7 higher** (11.23 higher to 14.17 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c,d]	none	10/24 (41.7%)	4/26 (15.4%)	**RR 2.71** (0.98 to 7.50)	**263 more per 1,000** (from 3 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	18/24 (75.0%)	18/26 (69.2%)	**RR 1.08** (0.77 to 1.53)	**55 more per 1,000** (from 159 fewer to 367 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c,d]	none	2/24 (8.3%)	6/26 (23.1%)	**RR 0.36** (0.08 to 1.62)	**148 fewer per 1,000** (from 143 more to 212 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	24	26	-	MD **0.31 higher** (0.13 lower to 0.75 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

b. All patients FEV1 reported from ≥70 to ≤90%.

c. 95% CI crosses line of no effect.

d. Few events.

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Recommendation 19

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 150 mg BID ; Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID ; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID ; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 18 years and older with CF mutation R117H (Moss 2015).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor
Any pulmonary exacerbation - Ivacaftor 150 mg BID follow up: 24 weeks	69 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 0.87** (0.45 to 1.67)	Study population	
				371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3)	50 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3) was **0**	MD **5 higher** (4.25 higher to 5.75 higher)

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Scale from: 0 to 90 follow up: 24 weeks					
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	50 (1 RCT)	⊕⊕⊕◯ MODERATE[b]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) was **0**	MD **12.7 higher** (11.23 higher to 14.17 higher)
Upper respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[b c d]	**RR 2.71** (0.98 to 7.50)	Study population	
				154 per 1,000	**263 more per 1,000** (3 fewer to 1,000 more)
Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[b c]	**RR 1.08** (0.77 to 1.53)	Study population	
				692 per 1,000	**55 more per 1,000** (159 fewer to 367 more)
Any serious adverse event - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[b c d]	**RR 0.36** (0.08 to 1.62)	Study population	
				231 per 1,000	**148 fewer per 1,000** (212 fewer to 143 more)
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3)	50 (1 RCT)	⊕⊕◯◯ LOW[b c]	-	The mean nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) was **0**	MD **0.31 higher** (0.13 lower to 0.75 higher)

		Scale from: 12 to 40 follow up: 24 weeks a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. b. All patients FEV1 reported from ≥70 to ≤90%. c. 95% CI crosses line of no effect. d. Few events. **Additional considerations:** The evidence is based on one study. Exacerbations improved but imprecise. No other improvements. Sweat chloride improved, although not determined by the panel to be a critical outcome. The panel decided on trivial for the effect of the desirable outcomes. The panel determined that there is possibly small undesirable effects.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** Panel agrees to not rate down for indirectness of FEV1 in the population.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Research evidence:** No research evidence identified. **Additional considerations:** The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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	○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** The panel determined that the balance of outcomes probably favors ivacaftor.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
			the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR guideline panel suggests ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Moderate certainty in the evidence* Remarks:				

	-R117H mutation shows large variability in clinical outcomes.
JUSTIFICATION	The R117H mutation shows enough variability to warrant a conditional recommendation even with moderate certainty in the evidence. This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H and likely reflect relative lung function. The overall consensus of the group was that patients and providers would be more likely to use this medication in this situation where more severe disease or more rapidly progressive disease is present.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 19

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a,b]	serious [c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕⊕◯◯ LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3) (follow up: 24 weeks; Scale from: 0 to 90)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [b]	not serious	none	24	26	-	MD **5 higher** (4.25 higher to 5.75 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [b]	not serious	none	24	26	-	MD **12.7 higher** (11.23 higher to 14.17 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [b]	serious [c,d]	none	10/24 (41.7%)	4/26 (15.4%)	**RR 2.71** (0.98 to 7.50)	**263 more per 1,000** (from 3 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	18/24 (75.0%)	18/26 (69.2%)	**RR 1.08** (0.77 to 1.53)	**55 more per 1,000** (from 159 fewer to 367 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [b]	serious [c,d]	none	2/24 (8.3%)	6/26 (23.1%)	**RR 0.36** (0.08 to 1.62)	**148 fewer per 1,000** (from 143 more to 212 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 40)												
1	randomized trials	not serious	not serious	serious [b]	serious [c]	none	24	26	-	MD **0.31 higher** (0.13 lower to 0.75 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

b. All patients FEV1 reported from ≥70 to ≤90%.

c. 95% CI crosses line of no effect.

d. Few events.

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Recommendation 20

Should **ivacaftor** vs. **no treatment** be used for **individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation**?

POPULATION:	individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation	**BACKGROUND:**	CFTR modulators are a new class of drugs that act by improving function of the defective cystic fibrosis transmembrane regulator (CFTR) protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. *In vitro* studies demonstrated that IVA increases CFTR open channel probability in cells expressing CFTR. IVA was designed to treat persons with mutation G551D, which is a gating mutation. A number of less common genotypes share the same gating defect as G551D (Class III mutation), and would be expected to have a similar response to IVA therapy. R117H is also a gating mutation with high variability of the penetrance of disease among individuals with this mutation. R117H impairs CFTR channel conductance and reduces channel gating.
INTERVENTION:	ivacaftor		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3); Any pulmonary exacerbation - Ivacaftor 150 mg BID (MID: 4); Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4); Upper respiratory symptoms - Ivacaftor 150 mg BID; Lower respiratory symptoms - Ivacaftor 150 mg BID; Cough - Ivacaftor 150 mg BID; Any serious adverse event - Ivacaftor 150 mg BID ; Any adverse event - Ivacaftor 150 mg BID; Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 10);		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

<table>
<tr><th></th><th>JUDGEMENT</th><th>RESEARCH EVIDENCE</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Research evidence:

Approximately 30,000 people in the US have been diagnosed with CF, of those one in 20 have been identified as unaffected carriers. R117H is the second most common gating mutation, after G551D. R117H is present in approximately 2.8 percent of individuals with CF entered in the CFF registry. Persons with the CF mutation R117H would be expect to have a similar response to IVA therapy as persons with a G551D mutation and are an important group to consider.

Additional considerations:

The research question was developed without regard to poly T genotype, since the panel elected to not discuss poly T status during the PICO development phase.</td></tr>
<tr><td>DESIRABLE EFFECTS</td><td rowspan="2">How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know</td><td rowspan="2">Research evidence:

One randomized controlled trial reported on ivacaftor vs no treatment among persons aged 6 years and older with CF mutation R117H (Moss 2015).

<table>
<tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr>
<tr><th>Risk with no treatment</th><th>Risk difference with ivacaftor</th></tr>
<tr><td>Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3)
Scale from: 0 to 150
follow up: 24 weeks</td><td>50
(1 RCT)</td><td>⨁⨁⨁◯
MODERATE[a]</td><td>-</td><td>The mean pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3) was 0</td><td>MD 5 higher (4.25 higher to 5.75 higher)</td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="2">Study population</td></tr>
</table>
</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td><td></td></tr>
</table>

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		Any pulmonary exacerbation - Ivacaftor 150 mg BID (MID: 4) follow up: 24 weeks	69 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 0.87** (0.45 to 1.67)	371 per 1,000	**48 fewer per 1,000** (204 fewer to 249 more)
		Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	50 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) was **0**	MD **12.7 higher** (11.23 higher to 14.17 higher)
		Upper respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[a c d]	**RR 2.71** (0.98 to 7.50)	Study population	
						154 per 1,000	**263 more per 1,000** (3 fewer to 1,000 more)
		Lower respiratory symptoms - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[a c]	**RR 1.08** (0.77 to 1.53)	Study population	
						692 per 1,000	**55 more per 1,000** (159 fewer to 367 more)
		Any serious adverse event - Ivacaftor 150 mg BID follow up: 24 weeks	50 (1 RCT)	⊕⊕◯◯ LOW[a c d]	**RR 0.36** (0.08 to 1.62)	Study population	
						231 per 1,000	**148 fewer per 1,000** (212 fewer to 143 more)
		Nutritional status as measured by BMI - Ivacaftor 150 mg BID	50 (1 RCT)	⊕⊕◯◯ LOW[a c]	-	The mean nutritional status as measured by BMI - Ivacaftor 150	MD **0.31 higher** (0.13 lower

		(MID: 0.3) Scale from: 12 to 40 follow up: 24 weeks | | | | mg BID (MID: 0.3) was **0** | to 0.75 higher) a. One patient in analysis with FEV1 >90%. All remaining with FEV1 <90%. b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26. c. 95% CI crosses line of no effect. d. Few events. **Additional considerations:** FEV1 level demonstrated both statistical and clinical benefit for persons with CF 18 years of age or older. The panel determined that there is possibly small undesirable effects. These include cataracts, liver function, and interference with oral contraceptives.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** For persons with FEV1 level greater than 90%, the panel agreed to rate the certainty of the evidence down for indirectness.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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	○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor list price as of 2015: $311,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US; however, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%, thus people outside of this range may not be able to get the drug. Other limiting criteria are things like having the indicated genotype, proof of improvement or maintenance on BMI and/or FEV1 while on drug, no presence of certain bacterial strains, compliance to this drug and/or other CF meds, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons age 6 years and older with the CF mutation G551D (whiting 2014): 1) after 96 weeks of treatment with ivacaftor FEV1 declined as the same rate as untreated persons; 2) after 96 weeks a 66% decline in FEV1; and 3) stable FEV1 over lifetime. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. Other assumptions used in the model include: with ivacaftor treatment FEV1 MD change in percentage points of 10.5 (95% CI: 8.5, 12.5), and cost of 182,000 pounds/year for ivacaftor. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor; however, if patients are ineligible for treatment or if treatment recommendations have not been developed for their genotype, then they might be disadvantaged. In addition, health coverage is variable by state.

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	● Varies ○ Don't know	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care- taker effort or burden of care. Additionally, adherence to oral medication instead of nebulized medication might be easier for the patient.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

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	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor vs. no treatment be used in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor vs no treatment in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation. *Conditional recommendation, Moderate certainty in the evidence* Remarks:				

	-Ivacaftor suggests benefit; however, there are unknown long-term harms. -Ivacaftor may provide benefit for patients who are symptomatic or lower FEV1 level -Cost needs to be considered.
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The balance between these values will vary widely among patients with R117H due to the high variability of clinical outcomes in individuals with this mutation. The overall consensus of the group was that patients and providers would be more likely to use this medication in situations where more symptomatic, more rapidly progressive disease or with a PPFEV1 at the lower end of this range (close to 90%), but would be less likely to use this therapy for more stable or minimal disease within this subgroup. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems. The panel held a vote to determine whether conditional for or against ivacaftor. Nine of the panel voted for ivacaftor and two against. While the limited evidence suggested benefit, there is still unknown harm of liver function and cataracts, and interactions with oral contraceptives.
SUBGROUP CONSIDERATIONS	The evidence did not provide enough information for a subgroup analysis on poly T status. The panel recognized variability in response to treatment within and between different poly T genotypes, increasing the uncertainty around the recommendation. This recommendation is directed at all persons with CF with the R117H mutation, not specific poly T genotypes.
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed to in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. Trials are needed to understand the efficacy of ivacaftor for persons with CF with the R117H mutation of different poly T genotypes.

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Evidence Profile for Recommendation 20

Ivacaftor compared to no treatment in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF with the R117H mutation

Setting: Outpatient

Bibliography: Moss RB, Flume PA, Elborn JS, Cooke J, Rowe SM, McColley SA, Rubenstein RC, Higgins M, on behalf of the VX11-770-110 (KONDUCT) study group. (2015). Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomized controlled trial. Lancet Respiratory Medicine. 3:524-33.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 150 mg BID (MID: 3) (follow up: 24 weeks; Scale from: 0 to 150)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	24	26	-	MD **5 higher** (4.25 higher to 5.75 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Any pulmonary exacerbation - Ivacaftor 150 mg BID (MID: 4) (follow up: 24 weeks)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious [a]	serious [b,c]	none	11/34 (32.4%)	13/35 (37.1%)	**RR 0.87** (0.45 to 1.67)	**48 fewer per 1,000** (from 204 fewer to 249 more)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 150 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious	serious [a]	not serious	none	24	26	-	MD **12.7 higher** (11.23 higher to 14.17 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [c,d]	none	10/24 (41.7%)	4/26 (15.4%)	**RR 2.71** (0.98 to 7.50)	**263 more per 1,000** (from 3 fewer to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - Ivacaftor 150 mg BID (follow up: 24 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomized trials	not serious	not serious	serious [a]	serious [c]	none	18/24 (75.0%)	18/26 (69.2%)	**RR 1.08** (0.77 to 1.53)	**55 more per 1,000** (from 159 fewer to 367 more)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - Ivacaftor 150 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious	serious [a]	serious [c,d]	none	2/24 (8.3%)	6/26 (23.1%)	**RR 0.36** (0.08 to 1.62)	**148 fewer per 1,000** (from 143 more to 212 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - Ivacaftor 150 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 40)												
1	randomized trials	not serious	not serious	serious [a]	serious [c]	none	24	26	-	MD **0.31 higher** (0.13 lower to 0.75 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. One patient in analysis with FEV1 >90%. All remaining with FEV1 <90%.

b. Outcome includes events reported across all age groups. Pulmonary exacerbations reported for 6-11 years: ivacaftor 2/9, placebo 1/8; 18 and older: ivacaftor 11/24, placebo 13/26.

c. 95% CI crosses line of no effect.

d. Few events.

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Recommendation 21

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 0-5 years with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 0-5 years with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). Ivacaftor is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. Lumacaftor therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Any pulmonary exacerbation - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Respiratory symptoms - cough - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level - ivacaftor 250 mg BID; Microbiological profile as measured by incidence of pseudomonas - ivacaftor 250 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?**	**Research evidence:**

	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 50% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Research evidence:** No randomized controlled trials that assessed treatment with lumacaftor and ivacaftor vs no treatment for persons aged 0-5 years with two copies of F508del mutation were identified. A single open-label trial (n=58) assessed the safety, tolerability, pharmacodynamics, and efficacy of treatment with lumacaftor and ivacaftor for persons aged 6-11 years with two copies of F508del mutation (Milla 2016). The controls from a randomized controlled trial were used to represent the no treatment/standard of care arm (Elborn 2016).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID was **0**	MD **2.9 higher** (0.26 higher to 5.54 higher)
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **4.5 higher** (0.58 higher to 8.42 higher)
				Study population	

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Any pulmonary exacerbation - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.43** (0.26 to 0.72)	481 per 1,000	**274 fewer per 1,000** (356 fewer to 135 fewer)
Any adverse event - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 0.96** (0.91 to 1.02)	Study population	
				985 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)
Nutritional status as measured by BMI - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.54 higher** (0.36 higher to 0.72 higher)
Upper respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 1.22** (0.93 to 1.59)	Study population	
				439 per 1,000	**97 more per 1,000** (31 fewer to 259 more)
Lower respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.24** (0.14 to 0.40)	Study population	
				864 per 1,000	**656 fewer per 1,000** (743 fewer to 518 fewer)

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).
b. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbation and lower respiratory symptoms are reduced. Pulmonary function, QoL, and BMI are increased based on the results.

The control group from Elborn 2016 may contain sicker patients and over inflate the effect of treatment from Milla 2016.

		Additional potential harms include cataracts and the need for frequent monitoring. There is uncertainty about long-term harms of treatment.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to use the open-label trial of Milla compared with the control group from a randomized trial (Elborn). Based on the comparison there are some concerns about indirectness of the Elborn evidence to this age group. Milla 2016 does not include persons with FEV1 level less than 40% or persons with CF ages 0-5. Within this age group there are changes at a very early age when monitored with CT scan or lung clearance. The panel discussed concerns of indirectness based on age group from Elborn or using a control group from a study with persons with CF and the mutation of G551D. The panel decided that there is less indirectness from a different age group than a different CF mutation patient group.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have normal lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on concerns about potential long-term adverse events and the very low certainty the evidence, the panel is uncertain about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced	**Research evidence:** No research evidence identified. **Additional considerations:**

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	○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment or if treatment formulations not been developed, then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care. Ivacaftor/lumacaftor treatment has not received FDA approval for children ages 0-5 years, which makes it not feasible to prescribe.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	**No**	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 0-5 years with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	o	o	o	o	o
RECOMMENDATION	Formulation is not available for children under 5 years of age for the ivacaftor/lumacaftor combination.				

JUSTIFICATION	The CFTR guideline panel recognized that there might be a benefit to children under 5 years of age based on the evidence from Milla et al., 2016; however, at the time of these recommendations there is no age-appropriate formulation. The panel voted in favor of not addressing as a recommendation in the document but including information in the limitations and future directions to highlight current practices and on-going studies that would inform the updates on these recommendations. Three panel members were absent from the voting.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 21

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 0-5 years with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine. Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., & Rosenfeld, M. (2016). Lumacaftor/ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis Homozygous for F508del-CFTR. American Journal of Respiratory and Critical Care Medicine, (ja).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **2.9 higher** (0.26 higher to 5.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **4.5 higher** (0.58 higher to 8.42 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Any pulmonary exacerbation - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	162/337 (48.1%)	**RR 0.43** (0.26 to 0.72)	**274 fewer per 1,000** (from 135 fewer to 356 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse event - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	55/58 (94.8%)	332/337 (98.5%)	**RR 0.96** (0.91 to 1.02)	**39 fewer per 1,000** (from 20 more to 89 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	31/58 (53.4%)	148/337 (43.9%)	**RR 1.22** (0.93 to 1.59)	**97 more per 1,000** (from 31 fewer to 259 more)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	291/337 (86.4%)	**RR 0.24** (0.14 to 0.40)	**656 fewer per 1,000** (from 518 fewer to 743 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **0.54 higher** (0.36 higher to 0.72 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).

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b. 95% CI crosses line of no effect

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Recommendation 22

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - Ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Any pulmonary exacerbation - ivacaftor 250 mg BID; Any serious adverse event - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Respiratory symptoms - cough - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level - ivacaftor 250 mg BID; Microbiological profile as measured by incidence of pseudomonas - ivacaftor 250 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials that assessed treatment with lumacaftor and ivacaftor vs no treatment for persons aged 0-5 years with two copies of F508del mutation were identified. A single open-label trial (n=58) assessed the safety, tolerability, pharmacodynamics, and efficacy of treatment with lumacaftor and ivacaftor for persons aged 6-11 years with two copies of F508del mutation (Milla 2016). The controls from a randomized controlled trial were used to represent the no treatment/standard of care arm (Elborn 2016).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID was **0**	MD **2.9 higher** (0.26 higher to 5.54 higher)
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **4.5 higher** (0.58 higher to 8.42 higher)

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Any pulmonary exacerbation - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.43** (0.26 to 0.72)	Study population		
				481 per 1,000	**274 fewer per 1,000** (356 fewer to 135 fewer)	
Any adverse event - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 0.96** (0.91 to 1.02)	Study population		
				985 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)	
Upper respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 1.22** (0.93 to 1.59)	Study population		
				439 per 1,000	**97 more per 1,000** (31 fewer to 259 more)	
Lower respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.24** (0.14 to 0.40)	Study population		
				864 per 1,000	**656 fewer per 1,000** (743 fewer to 518 fewer)	
Nutritional status as measured by BMI - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.54 higher** (0.36 higher to 0.72 higher)	

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).
b. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbation and lower respiratory symptoms are reduced. Pulmonary function, QoL, and BMI are increased based on the results.

The control group from Elborn 2016 may contain sicker patients and over inflate the effect of treatment from Milla 2016.

		Additional potential harms include cataracts and the need for frequent monitoring. There is uncertainty about long-term harms of treatment.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to use the open-label trial of Milla compared with the control group from a randomized trial (Elborn). Based on the comparison there are some concerns about indirectness of the Elborn evidence to this age group. Milla 2016 does not include persons with FEV1 level less than 40%. The panel discussed concerns of indirectness based on age group from Elborn or using a control group from a study with persons with CF and the mutation of G551D. The panel decided that there is less indirectness from a different age group than a different CF mutation patient group.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a normal lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertain about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?**	**Research evidence:** No research evidence identified.

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	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	CFTR panel suggests ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation. *Conditional recommendation, Very low certainty in the evidence*				

	Remarks: -Persons with FEV1 levels of less than 40% predicted might show benefit
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there are no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the committee elected to make a conditional recommendation for therapy. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. Other considerations may include cost, convenience, and the potential for unknown adverse effects. Four panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions.

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Evidence Profile for Recommendation 22

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 6-11 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine. Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., & Rosenfeld, M. (2016). Lumacaftor/ivacaftor in Patients Aged 6-11 Years With Cystic Fibrosis Homozygous for F508del-CFTR. American Journal of Respiratory And Critical Care Medicine, (ja).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **2.9 higher** (0.26 higher to 5.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **4.5 higher** (0.58 higher to 8.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Any pulmonary exacerbation - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	162/337 (48.1%)	**RR 0.43** (0.26 to 0.72)	**274 fewer per 1,000** (from 135 fewer to 356 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Any adverse event - ivacaftor 250 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	55/58 (94.8%)	332/337 (98.5%)	**RR 0.96** (0.91 to 1.02)	**39 fewer per 1,000** (from 20 more to 89 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	31/58 (53.4%)	148/337 (43.9%)	**RR 1.22** (0.93 to 1.59)	**97 more per 1,000** (from 31 fewer to 259 more)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	291/337 (86.4%)	**RR 0.24** (0.14 to 0.40)	**656 fewer per 1,000** (from 518 fewer to 743 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **0.54 higher** (0.36 higher to 0.72 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).

b. 95% CI crosses line of no effect

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Recommendation 23

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 (MID: 6.5); Quality of life as measured by CFQ-R respiratory domain score (MID: 4); Any pulmonary exacerbation; Adverse events; Upper respiratory symptoms; Lower respiratory symptoms; Respiratory symptoms - Cough; Nutritional status as measured by BMI (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials that assessed treatment with lumacaftor and ivacaftor vs no treatment for persons aged 0-5 years with two copies of F508del mutation were identified. A single open-label trial (n=58) assessed the safety, tolerability, pharmacodynamics, and efficacy of treatment with lumacaftor and ivacaftor for persons aged 6-11 years with two copies of F508del mutation (Milla 2016). The controls from a randomized controlled trial were used to represent the no treatment/standard of care arm (Elborn 2016).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Pulmonary function as measured by absolute change in percent predicted FEV1 (MID: 6.5) Scale from: 0 to 90 follow up: 24 weeks	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 (MID: 6.5) was **0**	MD **2.9 higher** (0.26 higher to 5.54 higher)
Quality of life as measured by CFQ-R respiratory domain score (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score (MID: 4) was **0**	MD **4.5 higher** (0.58 higher to 8.42 higher)

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Any pulmonary exacerbation follow up: 24 weeks	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.43** (0.26 to 0.72)	Study population		
				481 per 1,000	**274 fewer per 1,000** (356 fewer to 135 fewer)	
Adverse events	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 0.96** (0.91 to 1.02)	Study population		
				985 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)	
Upper respiratory symptoms follow up: 24 weeks	395 (1 observational study)	⊕◯◯◯ VERY LOW[a] [b]	**RR 1.22** (0.93 to 1.59)	Study population		
				439 per 1,000	**97 more per 1,000** (31 fewer to 259 more)	
Lower respiratory symptoms follow up: 24 weeks	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.24** (0.14 to 0.40)	Study population		
				864 per 1,000	**656 fewer per 1,000** (743 fewer to 518 fewer)	
Nutritional status as measured by BMI (MID: 0.3) Scale from: 12 to 22 follow up: 24 weeks	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean nutritional status as measured by BMI (MID: 0.3) was **0**	MD **0.54 higher** (0.36 higher to 0.72 higher)	

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).
b. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbation and lower respiratory symptoms are reduced. Pulmonary function, QoL, and BMI are increased based on the results.

The control group from Elborn 2016 may contain sicker patients and over inflate the effect of treatment from Milla 2016.

		Additional potential harms include cataracts and the need for frequent monitoring. There is uncertainty about long-term harms of treatment.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to use the open-label trial of Milla compared with the control group from a randomized trial (Elborn). Based on the comparison there are some concerns about indirectness of the Elborn evidence to this age group. The panel discussed concerns of indirectness based on age group from Elborn or using a control group from a study with persons with CF and the mutation of G551D. The panel decided that there is less indirectness from a different age group than a different CF mutation patient group.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have normal lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced	**Research evidence:** No research evidence identified. **Additional considerations:**

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	○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

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	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	Panel suggests ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation. *Conditional recommendation, Very low certainty in the evidence*				

JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there are no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the committee elected to suggest therapy based on a conditional recommendation. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. In other age groups, patients with better maintained lung function (PPFEV1 > 90%) did not experience the same relative benefit as those with lower lung function. Providers and families may take this into consideration discussing potential therapies. Other considerations may include cost, convenience, and the potential for unknown adverse effects. One panel member was absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 23

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 6-11 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine. Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., & Rosenfeld, M. (2016). Lumacaftor/Ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis Homozygous for F508del-CFTR. American Journal of Respiratory and Critical Care Medicine, (ja).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 (MID: 6.5) (follow up: 24 weeks; Scale from: 0 to 90)												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **2.9 higher** (0.26 higher to 5.54 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **4.5 higher** (0.58 higher to 8.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Any pulmonary exacerbation (follow up: 24 weeks)												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	162/337 (48.1%)	**RR 0.43** (0.26 to 0.72)	**274 fewer per 1,000** (from 135 fewer to 356 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	55/58 (94.8%)	332/337 (98.5%)	**RR 0.96** (0.91 to 1.02)	**39 fewer per 1,000** (from 20 more to 89 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Upper respiratory symptoms (follow up: 24 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	31/58 (53.4%)	148/337 (43.9%)	**RR 1.22** (0.93 to 1.59)	**97 more per 1,000** (from 31 fewer to 259 more)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms (follow up: 24 weeks)												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	291/337 (86.4%)	**RR 0.24** (0.14 to 0.40)	**656 fewer per 1,000** (from 518 fewer to 743 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Nutritional status as measured by BMI (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 22)												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **0.54 higher** (0.36 higher to 0.72 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).

b. 95% CI crosses line of no effect.

Recommendation 24

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Any pulmonary exacerbation - ivacaftor 250 mg BID; Any serious adverse event - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Respiratory symptoms - cough - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level - ivacaftor 250 mg BID; Microbiological profile as measured by incidence of pseudomonas - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials that assessed treatment with lumacaftor and ivacaftor vs no treatment for persons aged 0-5 years with two copies of F508del mutation were identified. A single open-label trial (n=58) assessed the safety, tolerability, pharmacodynamics, and efficacy of treatment with lumacaftor and ivacaftor for persons aged 6-11 years with two copies of F508del mutation (Milla 2016). The controls from a randomized controlled trial were used to represent the no treatment/standard of care arm (Elborn 2016).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID was **0**	MD **2.9 higher** (0.26 higher to 5.54 higher)
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **4.5 higher** (0.58 higher to 8.42 higher)

Any pulmonary exacerbation - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.43** (0.26 to 0.72)	Study population	
				481 per 1,000	**274 fewer per 1,000** (356 fewer to 135 fewer)
Any adverse event - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a b]	**RR 0.96** (0.91 to 1.02)	Study population	
				985 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)
Upper respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a b]	**RR 1.22** (0.93 to 1.59)	Study population	
				439 per 1,000	**97 more per 1,000** (31 fewer to 259 more)
Lower respiratory symptoms - ivacaftor 250 mg BID	395 (1 observational study)	⊕◯◯◯ VERY LOW[a]	**RR 0.24** (0.14 to 0.40)	Study population	
				864 per 1,000	**656 fewer per 1,000** (743 fewer to 518 fewer)
Nutritional status as measured by BMI - ivacaftor 250 mg BID	396 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.54 higher** (0.36 higher to 0.72 higher)

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).
b. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbation and lower respiratory symptoms are reduced. Pulmonary function, QoL, and BMI are increased based on the results.

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		The control group from Elborn 2016 may contain sicker patients and over inflate the effect of treatment from Milla 2016. Additional potential harms include cataracts and the need for frequent monitoring. There is uncertainty about long-term harms of treatment.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to use the open-label trial of Milla compared with the control group from a randomized trial (Elborn). Based on the comparison there are some concerns about indirectness of the Elborn evidence to this age group. The panel discussed concerns of indirectness based on age group from Elborn or using a control group from a study with persons with CF and the mutation of G551D. The panel decided that there is less indirectness from a different age group than a different CF mutation patient group.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have normal lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the very low certainty the evidence, the panel is uncertainty about the balance of desirable and undesirable effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?**	**Research evidence:** No research evidence identified.

	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation. *Conditional recommendation, Very low certainty in the evidence* Remarks: -Based on the indirectness of the population, may not expect to see the same effects in healthier persons.				

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JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The safety of IVA/LUM combination therapy in children age 6-11 years seems reasonably well established. As discussed above, there is no direct efficacy data available but extrapolation from older patient groups appears justified. For these reasons, the committee elected to suggest therapy based on a conditional recommendation. Differentiating recommendations based on PPFEV1 is not warranted, based on lack of evidence, but may be a consideration for prescribing providers. In other age groups, patients with better maintained lung function (PPFEV1 > 90%) did not experience the same relative benefit as those with lower lung function. Providers and families may take this into consideration when engaged in co-production for disease management. Other considerations may include cost, convenience, and the potential for unknown adverse effects. Four panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 24

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 6-11 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine. Milla, C. E., Ratjen, F., Marigowda, G., Liu, F., Waltz, D., & Rosenfeld, M. (2016). Lumacaftor/ivacaftor in Patients Aged 6-11 Years with Cystic Fibrosis Homozygous for F508del-CFTR. American Journal of Respiratory and Critical Care Medicine, (ja).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **2.9 higher** (0.26 higher to 5.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **4.5 higher** (0.58 higher to 8.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Any pulmonary exacerbation - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	162/337 (48.1%)	**RR 0.43** (0.26 to 0.72)	**274 fewer per 1,000** (from 135 fewer to 356 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Any adverse event - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	55/58 (94.8%)	332/337 (98.5%)	**RR 0.96** (0.91 to 1.02)	**39 fewer per 1,000** (from 20 more to 89 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	serious [a]	serious [b]	none	31/58 (53.4%)	148/337 (43.9%)	**RR 1.22** (0.93 to 1.59)	**97 more per 1,000** (from 31 fewer to 259 more)	⊕◯◯◯ VERY LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	12/58 (20.7%)	291/337 (86.4%)	**RR 0.24** (0.14 to 0.40)	**656 fewer per 1,000** (from 518 fewer to 743 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID												
1	observational studies	not serious	not serious	serious [a]	not serious	none	58	338	-	MD **0.54 higher** (0.36 higher to 0.72 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

a. Milla 2016 includes persons with mean baseline FEV1 91.4 (SD: 13.7); Comparison is control group from Elborn 2016 includes persons mean age: 25 years (range: 12 - 57 years).

b. 95% CI crosses line of no effect.

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Recommendation 25

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - Ivacaftor 250 mg BID; Any serious adverse event - ivacaftor 250 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5); Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4); Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Cough - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported a subgroup analysis of persons with F508del homozygous mutation and a baseline FEV1 of 40% (Elborn 2016).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.71** (0.50 to 1.02)	Study population	
				714 per 1,000	**207 fewer per 1,000** (357 fewer to 14 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) Scale from: 0 to 90	109 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) was **0**	MD **3.51 higher** (3.01 higher to 4.01 higher)

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		follow up: 24 weeks				
		Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	109 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) was **0**	MD **0.78 lower** (2.01 lower to 0.45 higher)
		Upper respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 1.65** (0.86 to 3.17)	Study population	
						286 per 1,000	**186 more per 1,000** (40 fewer to 620 more)
		Lower respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	Among persons in the treatment group (n=53), 58 lower respiratory symptoms were reported. Among 28 controls, 27 events were reported. This included cough, dyspnea, and increased sputum.	
		Any adverse event - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.99** (0.93 to 1.06)	Study population	
						1,000 per 1,000	**10 fewer per 1,000** (70 fewer to 60 more)
		Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3) Scale from: 12 to	109 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean nutritional status as measured by BMI - ivacaftor	MD **0.46 higher** (0.38 higher to 0.53 higher)

		28 follow up: 24 weeks | | | | 250 mg BID (MID: 0.3) was **0** |

a. Mean age: 27 years (13 - 44 years).
b. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbations may be reduced. Pulmonary function and BMI are increased based on the results from the TRAFFIC and TRANSPORT studies.

Additional potential harms include cataracts and the need for frequent monitoring.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness based on the age of the study population.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Additional considerations:** For this group, even a small benefit would be of value to the patient. The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

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BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** For persons with lower FEV1 level and lung function, this treatment may provide greater benefit.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.

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EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify

	○ Don't know	barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	

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	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●

RECOMMENDATION	The CFTR guideline panel recommends ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation. *Strong recommendation, Moderate certainty in the evidence*
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although the two trials had very large numbers of participants, there were relatively few patients age 12-17 years. Nonetheless, the committee felt that the numbers were sufficient to suggest a moderate degree of certainty of moderate benefit, warranting a strong recommendation for therapy. Another important consideration was the potential for long term stabilization of lung function. The prognosis for a patient age 12-17 years with PPFEV1 < 40% is not good. The committee felt, once again, that short term improvements in PPFEV1 and BMI, though perhaps not clinically significant, suggested that significant long term benefits were likely and that the balance between desirable and undesirable effects favored treatment. The committee did note, however, that there are anecdotal reports of increased cough and chest tightness among patients of all ages with PPFEV1 < 40%. Two panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 25

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 12-17 years and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	27/53 (50.9%)	20/28 (71.4%)	**RR 0.71** (0.50 to 1.02)	**207 fewer per 1,000** (from 14 more to 357 fewer)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event - ivacaftor 250 mg BID												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	148/738 (20.1%)	212/740 (28.6%)	**RR 0.70** (0.57 to 0.87)	**86 fewer per 1,000** (from 37 fewer to 123 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) (follow up: 24 weeks; Scale from: 0 to 40)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **3.51 higher** (3.01 higher to 4.01 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **0.78 lower** (2.01 lower to 0.45 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	25/53 (47.2%)	8/28 (28.6%)	**RR 1.65** (0.86 to 3.17)	**186 more per 1,000** (from 40 fewer to 620 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	Among persons in the treatment group (n=53), 58 lower respiratory symptoms were reported. Among 28 controls, 27 events were reported. This included cough, dyspnea, and increased sputum.				⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 28)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **0.46 higher** (0.38 higher to 0.53 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Elborn subgroup analysis counts controls twice.

b. Mean age: 27 years (13 - 44 years).

c. 95% CI crosses line of no effect.

Recommendation 26

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - ivacaftor 250 mg BID; Any serious adverse event - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5); Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4); Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Cough - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3); Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score; Pulmonary function as measured by relative change in percent predicted FEV1 - ivacaftor 250 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

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	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	**Research evidence:** Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Research evidence:** Two studies present on results from TRAFFIC and TRANSPORT three-arm randomized controlled trials (Elborn 2016, Wainwright 2015). Data from Wainwright was used to inform this question, as it contained the more comprehensive dataset.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation - ivacaftor 250 mg BID follow up: 24 weeks	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.76** (0.66 to 0.88)	Study population	
				492 per 1,000	**118 fewer per 1,000** (167 fewer to 59 fewer)
Any serious adverse event - ivacaftor 250 mg BID follow up: 24 weeks	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.70** (0.54 to 0.91)	Study population	
				286 per 1,000	**86 fewer per 1,000** (132 fewer to 26 fewer)

		Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) Scale from: 0 to 90 follow up: 24 weeks	1084 (2 RCTs)	⊕⊕◯◯ LOW[a] [b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) was **0**	MD **3.06 higher** (2.4 higher to 3.72 higher)
		Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) Scale from: 0 to 100 follow up: 24 weeks	1076 (2 RCTs)	⊕⊕◯◯ LOW[a] [c]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) was **0**	MD **2.61 higher** (1.63 higher to 3.59 higher)
		Upper respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	1108 (2 RCTs)	⊕⊕◯◯ LOW[a] [d]	**RR 1.06** (0.91 to 1.22)	Study population	
						422 per 1,000	**25 more per 1,000** (38 fewer to 93 more)
		Lower respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.89** (0.80 to 0.99)	Study population	
						668 per 1,000	**73 fewer per 1,000** (134 fewer to 7 fewer)
		Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3)	1081 (2 RCTs)	⊕⊕◯◯ LOW[a] [b]	-	The mean nutritional status as measured by BMI - ivacaftor 250	MD **0.27 higher** (0.13 higher to 0.4 higher)

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		Scale from: 12 to 28 follow up: 24 weeks | | | | mg BID (MID: 0.3) was **0** | | a. Mean age: 25 years (range: 12 - 57 years) b. I2 = 100%. c. I2 = 98%. d. 95% CI crosses line of no effect. **Additional considerations:** Pulmonary exacerbation and serious adverse events are reduced. Pulmonary function, QoL, and BMI are also increased based on the results from the TRAFFIC and TRANSPORT studies. Additional potential harms include cataracts and the need for frequent monitoring.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to not rate down for indirectness even though the age range spans beyond 12-17 years (mean age is 25 years with a range of 12 to 57 years).
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	**Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

	○ No known undesirable outcomes	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?**	**Research evidence:** No research evidence identified.

	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	The CFTR guideline panel recommends ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation. *Strong recommendation, Moderate certainty in the evidence*				

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JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Very large numbers of patients age 12-17 years with PPFEV1 40-90% were included in the two trials. Clinically-important improvements were noted in most patient-important clinical outcomes. Hence, the committee felt that there was a moderate degree of certainty of moderate benefit. A relatively low degree of concern regarding potential adverse effects resulted in a strong recommendation for therapy. Of course, decisions to treat individual patients must be based upon patient-specific factors. Considerations should include PPFEV1 (there may be a greater rationale to treat a patient with PPFEV1 of 40% compared to a patient with PPFEV1 of 90%), comorbidities (e.g. liver disease), patient/family desires (co-production), and concerns over potential adverse effects. Two panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 26

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 12-17 years and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., ... & Konstan, M. W. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. New England Journal of Medicine, 373(3), 220-231.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - ivacaftor 250 mg BID (follow up: 24 weeks)												
2	randomized trials	not serious	not serious	serious [a]	not serious	none	277/738 (37.5%)	182/370 (49.2%)	**RR 0.76** (0.66 to 0.88)	**118 fewer per 1,000** (from 59 fewer to 167 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any serious adverse event - ivacaftor 250 mg BID (follow up: 24 weeks)												
2	randomized trials	not serious	not serious	serious [a]	not serious	none	148/738 (20.1%)	106/370 (28.6%)	**RR 0.70** (0.54 to 0.91)	**86 fewer per 1,000** (from 26 fewer to 132 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (MID: 3.5) (follow up: 24 weeks; Scale from: 0 to 90)												
2	randomized trials	not serious	serious [b]	serious [a]	not serious	none	721	363	-	MD **3.06 higher** (2.4 higher to 3.72 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (MID: 4) (follow up: 24 weeks; Scale from: 0 to 100)												
2	randomized trials	not serious	serious [c]	serious [a]	not serious	none	707	369	-	MD **2.61 higher** (1.63 higher to 3.59 higher)	⊕⊕◯◯ LOW	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												
2	randomized trials	not serious	not serious	serious [a]	serious [d]	none	329/738 (44.6%)	156/370 (42.2%)	**RR 1.06** (0.91 to 1.22)	**25 more per 1,000** (from 38 fewer to 93 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	serious [a]	not serious	none	437/738 (59.2%)	247/370 (66.8%)	**RR 0.89** (0.80 to 0.99)	**73 fewer per 1,000** (from 7 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID (MID: 0.3) (follow up: 24 weeks; Scale from: 12 to 28)												
2	randomized trials	not serious	serious [b]	serious [a]	not serious	none	714	367	-	MD **0.27 higher** (0.13 higher to 0.4 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Mean age: 25 years (range: 12 - 57 years)

b. I2 = 100%.

c. I2 = 98%.

d. 95% CI crosses line of no effect.

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Recommendation 27

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - ivacaftor 250 mg BID; Any serious adverse event - ivacaftor 250 mg BID; Any adverse event - ivacaftor 250 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Respiratory symptoms - cough - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level - ivacaftor 250 mg BID; Microbiological profile as measured by incidence of pseudomonas - ivacaftor 250 mg BID; Burden of care as measured by CFQ-R treatment burden domain score - ivacaftor 250 mg BID;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

No randomized controlled trials addressed whether lumacaftor with ivacaftor or no treatment should be used among patients with CF and two copies of the F508del mutation with FEV1 greater than 90%. Two randomized trials reported on ivacaftor/lumacaftor vs no treatment among the population of interest with FEV1 between 40% and 90% (Boyle 2014, Elborn 2016, Wainwright 2015).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation - ivacaftor 250 mg BID	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a] [b]	**RR 0.76** (0.66 to 0.88)	Study population	
				492 per 1,000	**118 fewer per 1,000** (167 fewer to 59 fewer)
Any serious adverse event - ivacaftor 250 mg BID	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a] [b]	**RR 0.70** (0.54 to 0.91)	Study population	
				286 per 1,000	**86 fewer per 1,000** (132 fewer to 26 fewer)
Pulmonary function as measured by absolute change in percent predicted	1084 (2 RCTs)	⊕⊕◯◯ LOW[a] [b] [c]	-	The mean pulmonary function as measured by absolute change in percent predicted	MD **3.06 higher** (2.4 higher to 3.72 higher)

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FEV1 - ivacaftor 250 mg BID				FEV1 - ivacaftor 250 mg BID was **0**	
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID	1076 (2 RCTs)	⊕⊕◯◯ LOW[a b d]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **2.61 higher** (1.63 higher to 3.59 higher)
Upper respiratory symptoms - ivacaftor 250 mg BID	1108 (2 RCTs)	⊕⊕◯◯ LOW[a b e]	**RR 1.06** (0.91 to 1.22)	Study population	
				422 per 1,000	**25 more per 1,000** (38 fewer to 93 more)
Lower respiratory symptoms - ivacaftor 250 mg BID	1108 (2 RCTs)	⊕⊕⊕◯ MODERATE[a b]	**RR 0.89** (0.80 to 0.99)	Study population	
				668 per 1,000	**73 fewer per 1,000** (134 fewer to 7 fewer)
Nutritional status as measured by BMI - ivacaftor 250 mg BID	1081 (2 RCTs)	⊕⊕⊕◯ MODERATE[a b]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.27 higher** (0.13 higher to 0.4 higher)

a. Mean age: 25 years (range: 12 - 57 years)
b. FEV1 level ranges from 40% to 90%.
c. I2 = 100%.
d. I2 = 98%.
e. 95% CI crosses line of no effect.

Additional considerations:

Pulmonary exacerbation and serious adverse events are reduced. Pulmonary function, QoL, and BMI are also increased based on the results from the TRAFFIC and TRANSPORT studies.

Additional potential harms include cataracts and the need for frequent monitoring.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel decided to rate down for indirectness based on age and FEV1 level.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies	

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	○ Don't know	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.

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ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	

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	JUDGEMENT							IMPLICATIONS
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The CFTR panel suggests ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation. *Conditional recommendation, Low certainty in the evidence* Remarks: -Based on the indirectness of the population, may not expect to see the same effects in healthier persons.				
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. As above, there is no data directly informing a decision to treat patients age 12-17 years and PPFEV1 > 90%.				

	However, extrapolation of data from patients in this age group with lower PPFEV1 and adult patients with PPFEV1 > 90% led the committee to suggest treatment rather than no treatment for these patients. The committee believed that there is no reason for patients meeting these demographic criteria to respond differently to treatment than similar patients of different ages or with lower PPFEV1. Additionally, the committee believed that a low level of concern regarding potential adverse effects favored treatment in the light of the known disease severity of the homozygous F508del genotype. Lastly, the potential for long term treatment with combination IVA/LUM to decrease the rate of decline of PPFEV1 suggests that patients age 12-17 years and PPFEV1 > 90% will benefit from therapy. Two panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 27

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 12-17 years and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., ... & Konstan, M. W. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. New England Journal of Medicine, 373(3), 220-231.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - ivacaftor 250 mg BID												
2	randomized trials	not serious	not serious	serious [a,b]	not serious	none	277/738 (37.5%)	182/370 (49.2%)	**RR 0.76** (0.66 to 0.88)	**118 fewer per 1,000** (from 59 fewer to 167 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any serious adverse event - ivacaftor 250 mg BID												
2	randomized trials	not serious	not serious	serious [a,b]	not serious	none	148/738 (20.1%)	106/370 (28.6%)	**RR 0.70** (0.54 to 0.91)	**86 fewer per 1,000** (from 26 fewer to 132 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID												
2	randomized trials	not serious	serious [c]	serious [a,b]	not serious	none	721	363	-	MD **3.06 higher** (2.4 higher to 3.72 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID												
2	randomized trials	not serious	serious [d]	serious [a,b]	not serious	none	707	369	-	MD **2.61 higher** (1.63 higher to 3.59 higher)	⊕⊕◯◯ LOW	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID												
2	randomized trials	not serious	not serious	serious [a,b]	serious [e]	none	329/738 (44.6%)	156/370 (42.2%)	**RR 1.06** (0.91 to 1.22)	**25 more per 1,000** (from 38 fewer to 93 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms - ivacaftor 250 mg BID												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	not serious	not serious	serious [a,b]	not serious	none	437/738 (59.2%)	247/370 (66.8%)	**RR 0.89** (0.80 to 0.99)	**73 fewer per 1,000** (from 7 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID												
2	randomized trials	not serious	not serious	serious [a,b]	not serious	none	714	367	-	MD **0.27 higher** (0.13 higher to 0.4 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Mean age: 25 years (range: 12 - 57 years)

b. FEV1 level ranges from 40% to 90%.

c. I2 = 100%.

d. I2 = 98%.

e. 95% CI crosses line of no effect.

Recommendation 28

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation - ivacaftor 250 mg BID; Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Upper respiratory symptoms - ivacaftor 250 mg BID; Lower respiratory symptoms - ivacaftor 250 mg BID; Cough - ivacaftor 250 mg BID; Any serious adverse event; Any adverse event - ivacaftor 250 mg BID; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

JUDGEMENT	RESEARCH EVIDENCE

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PROBLEM

Is the problem a priority?

○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know

Research evidence:

Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.

DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know

UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know

Research evidence:

One randomized controlled trial reported a subgroup analysis of persons with F508del homozygous mutation and a baseline FEV1 of 40% (Elborn 2016).

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a] [b]	**RR 0.71** (0.50 to 1.02)	Study population	
				714 per 1,000	**207 fewer per 1,000** (357 fewer to 14 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID follow up: 24 weeks	109 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID was **0**	MD **3.51 higher** (3.01 higher to 4.01 higher)

Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID follow up: 24 weeks	109 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **0.78 lower** (2.01 lower to 0.45 higher)
Upper respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 1.65** (0.86 to 3.17)	Study population	
				286 per 1,000	**186 more per 1,000** (40 fewer to 620 more)
Lower respiratory symptoms - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	-	Among persons in the treatment group (n=53), 58 lower respiratory symptoms were reported. Among 28 controls, 27 events were reported. This included cough, dyspnea, and increased sputum.	
Any adverse event - ivacaftor 250 mg BID follow up: 24 weeks	81 (1 RCT)	⊕⊕◯◯ LOW[a b]	**RR 0.99** (0.93 to 1.06)	Study population	
				1,000 per 1,000	**10 fewer per 1,000** (70 fewer to 60 more)
Nutritional status as measured by BMI - ivacaftor 250 mg BID follow up: 24 weeks	109 (1 RCT)	-[a]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.46 higher** (0.38 higher to 0.53 higher)

a. Mean age: 27 years (13 - 44 years).
b. 95% CI crosses line of no effect.

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		Additional considerations: Pulmonary exacerbations may be reduced. Pulmonary function and BMI are increased based on the results from the TRAFFIC and TRANSPORT studies. Additional potential harms include cataracts and the need for frequent monitoring. Recent abstract submitted to the ATS meeting suggests intolerance of treatment as observed through coughing and chest tightness, as well as other adverse events.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed to not rate down for indirectness based on the age group of the participants in the study.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** For this group, even a small benefit would be of value to the patient. The panel decided that there is no important uncertainty or variability in how much people value the outcomes considered.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** For persons with lower FEV1 level and lung function, this treatment may provide greater benefit.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

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Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	The CFTR panel recommends ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation**.** *Strong recommendation, Moderate certainty in the evidence*				

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JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. Although the two RCTs had very large numbers of participants, there were relatively few patients age 18 years and older with a PPFEV1 < 40%. Nonetheless, the committee felt that the numbers were sufficient and there was enough generalizable data (from other age and PPFEV1 groups) to suggest a moderate degree of certainty of moderate benefit, warranting a strong recommendation for therapy. As with younger patients with significant disease burden, the committee believed that potential long term benefits outweigh potential adverse effects. The committee did note, however, that there are anecdotal reports of increased cough and chest tightness among patients of all ages with PPFEV1 < 40%. Consideration should be given to this and other potential issues prior to initiation of therapy. One panel member was absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

Evidence Profile for Recommendation 28

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 18 and older and FEV1 less than 40% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Elborn, J. S., Ramsey, B. W., Boyle, M. P., Konstan, M. W., Huang, X., Marigowda, G., ... & Wainwright, C. E. (2016). Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. The Lancet Respiratory Medicine.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ivacaftor/lumacaftor combination drug**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Any pulmonary exacerbation - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	27/53 (50.9%)	20/28 (71.4%)	**RR 0.71** (0.50 to 1.02)	**207 fewer per 1,000** (from 14 more to 357 fewer)	⊕⊕◯◯ LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (follow up: 24 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **3.51 higher** (3.01 higher to 4.01 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **0.78 lower** (2.01 lower to 0.45 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Upper respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	25/53 (47.2%)	8/28 (28.6%)	**RR 1.65** (0.86 to 3.17)	**186 more per 1,000** (from 40 fewer to 620 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Lower respiratory symptoms - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	Among persons in the treatment group (n=53), 58 lower respiratory symptoms were reported. Among 28 controls, 27 events were reported. This included cough, dyspnea, and increased sputum.				⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse event - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	52/53 (98.1%)	28/28 (100.0%)	**RR 0.99** (0.93 to 1.06)	**10 fewer per 1,000** (from 60 more to 70 fewer)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID (follow up: 24 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	not serious	none	53	56	-	MD **0.46 higher** (0.38 higher to 0.53 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Elborn subgroup analysis counts controls twice.

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b. Mean age: 27 years (13 - 44 years).

c. 95% CI crosses line of no effect.

Recommendation 29

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation; Any serious adverse event; Any adverse event; Pulmonary function as measured by absolute change in percent predicted FEV1; Quality of life as measured by CFQ-R respiratory domain score - Ivacaftor 250 mg BID; Upper respiratory symptoms; Lower respiratory symptoms; Respiratory symptoms - cough; Nutritional status as measured by BMI - ivacaftor 250 mg BID; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?**	**Research evidence:**

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	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Research evidence:** Two studies present on results from TRAFFIC and TRANSPORT three-arm randomized controlled trials (Elborn 2016, Wainwright 2015). Data from Wainwright was used to inform this question, as it contained the more comprehensive dataset.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation follow up: range 8 weeks to 24 weeks	1207 (3 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.76** (0.66 to 0.87)	Study population	
				476 per 1,000	**114 fewer per 1,000** (162 fewer to 62 fewer)
Any serious adverse event follow up: range 8 weeks to 24 weeks	1207 (3 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.69** (0.56 to 0.85)	Study population	
				282 per 1,000	**87 fewer per 1,000** (124 fewer to 42 fewer)
Pulmonary function as measured by absolute change in percent predicted FEV1	1206 (3 RCTs)	⊕⊕◯◯ LOW[a b]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 was **0**	MD **3.92 higher** (3.33 higher to 4.52 higher)

follow up: range 8 weeks to 24 weeks					
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID follow up: range 8 weeks to 24 weeks	1172 (3 RCTs)	⊕⊕◯◯ LOW[a b]	-	The mean quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID was **0**	MD **7.33 higher** (5.95 higher to 8.71 higher)
Upper respiratory symptoms follow up: range 8 weeks to 24 weeks	1207 (3 RCTs)	⊕⊕◯◯ LOW[a c]	**RR 1.06** (0.93 to 1.22)	Study population	
				413 per 1,000	**25 more per 1,000** (29 fewer to 91 more)
Lower respiratory symptoms follow up: range 8 weeks to 24 weeks	1207 (3 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 0.90** (0.82 to 0.98)	Study population	
				647 per 1,000	**65 fewer per 1,000** (117 fewer to 13 fewer)
Nutritional status as measured by BMI - ivacaftor 250 mg BID follow up: 24 weeks	1081 (2 RCTs)	⊕⊕◯◯ LOW[a d]	-	The mean nutritional status as measured by BMI - ivacaftor 250 mg BID was **0**	MD **0.27 higher** (0.13 higher to 0.4 higher)

a. Mean age: 25 years (range: 12 - 57 years)
b. I2 = 98%.
c. 95% CI crosses line of no effect.
d. I2 = 100%.

Additional considerations:

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		Pulmonary exacerbation and serious adverse events are reduced. Pulmonary function, QoL, and BMI are also increased based on the results from the TRAFFIC and TRANSPORT studies. The panel voted on magnitude of desirable effects and decided on Moderate. Additional potential harms include cataracts and the need for frequent monitoring, as well as other drug interaction (e.g., hormonal contraceptives). There is uncertainty about long-term harms of treatment.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel thinks age group is direct for the question and did not rate down for indirectness. Some inconsistency acknowledged based on analysis techniques.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.

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CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children. Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?**	**Research evidence:** No research evidence identified.

	○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** Direct evidence assessing stakeholder acceptability to ivacaftor/lumacaftor was not identified. One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

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	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	●
RECOMMENDATION	The CFTR panel recommends for ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation. *Strong recommendation, Moderate certainty in the evidence*				

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JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The majority of patients in the three RCTs comparing treatment with the IVA/LUM combination drug versus no treatment were age 18 years and older with a PPFEV1 of 40-90%. Compelling evidence from these three trials demonstrates significant improvements in several patient-important clinical outcomes. The committee judged the clinical benefit to patients to be moderate to large with a moderate degree of certainty leading to a strong recommendation. The risk of adverse effects was felt to be small though there were some concerns raised. These included drug-drug interactions, impact of IVA/LUM on birth control, and potential unidentified long term adverse effects (e.g. liver disease). Consideration was also given to preliminary reports suggesting that the rate of decline of PPFEV1 may be decreased in patients treated with IVA/LUM. This suggests potential long term benefit and increases the benefit to risk ratio. Two panel members were absent during the discussion and recommendation.
SUBGROUP CONSIDERATIONS	
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.
MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function. An abstract presented at the ATS meeting may provide more information on potential harms of this therapy and should be reviewed in any updated recommendations.

Evidence Profile for Recommendation 29

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 18 and older and FEV1 40-90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., ... & Konstan, M. W. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. New England Journal of Medicine, 373(3), 220-231.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation (follow up: range 8 weeks to 24 weeks)												
3	randomized trials	not serious	not serious	serious [a]	not serious	none	285/810 (35.2%)	189/397 (47.6%)	**RR 0.76** (0.66 to 0.87)	**114 fewer per 1,000** (from 62 fewer to 162 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any serious adverse event (follow up: range 8 weeks to 24 weeks)												
3	randomized trials	not serious	not serious	serious [a]	not serious	none	155/810 (19.1%)	112/397 (28.2%)	**RR 0.69** (0.56 to 0.85)	**87 fewer per 1,000** (from 42 fewer to 124 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Pulmonary function as measured by absolute change in percent predicted FEV1 (follow up: range 8 weeks to 24 weeks)												
3	randomized trials	not serious	serious [b]	serious [a]	not serious	none	798	408	-	MD **3.92 higher** (3.33 higher to 4.52 higher)	⊕⊕◯◯ LOW	CRITICAL
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (follow up: range 8 weeks to 24 weeks)												
3	randomized trials	not serious	serious [b]	serious [a]	not serious	none	778	394	-	MD **7.33 higher** (5.95 higher to 8.71 higher)	⊕⊕◯◯ LOW	CRITICAL
Upper respiratory symptoms (follow up: range 8 weeks to 24 weeks)												
3	randomized trials	not serious	not serious	serious [a]	serious [c]	none	353/810 (43.6%)	164/397 (41.3%)	**RR 1.06** (0.93 to 1.22)	**25 more per 1,000** (from 29 fewer to 91 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms (follow up: range 8 weeks to 24 weeks)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	not serious	not serious	serious [a]	not serious	none	466/810 (57.5%)	257/397 (64.7%)	**RR 0.90** (0.82 to 0.98)	**65 fewer per 1,000** (from 13 fewer to 117 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Nutritional status as measured by BMI - ivacaftor 250 mg BID (follow up: 24 weeks)												
2	randomized trials	not serious	serious [d]	serious [a]	not serious	none	714	367	-	MD **0.27 higher** (0.13 higher to 0.4 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Mean age: 25 years (range: 12 - 57 years)

b. I2 = 98%.

c. 95% CI crosses line of no effect.

d. I2 = 100%.

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Recommendation 30

Should **ivacaftor/lumacaftor combination drug** vs. **no treatment** be used for **individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation**?

POPULATION:	individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation	**BACKGROUND:**	Cystic fibrosis transmembrane regulator (CFTR) modulators are a new class of drugs that act by improving function or increasing quantity of the defective CFTR protein. The indications and efficacy of these drugs depend upon the CFTR mutation in the individual patient. The first CFTR modulator approved for clinical use was ivacaftor (IVA). IVA is a potentiator of CFTR function. Ivacaftor was designed to treat persons with a gating mutation; however, has not been found to be effective when used for persons with F508del mutations. The F508del mutation interferes with CFTR protein folding and channel gating activity. Lumacaftor (LUM) is a CFTR modulator that partially corrects the folding defect in F508del-CFTR, resulting in slightly increased surface protein. LUM therapy alone is insufficient to increase F508del-CFTR activity to a level high enough to affect CF lung disease. However; when provided in combination, lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality.
INTERVENTION:	ivacaftor/lumacaftor combination drug		
COMPARISON:	no treatment		
MAIN OUTCOMES:	Any pulmonary exacerbation; Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID; Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID; Any serious adverse event; Any adverse event; Upper respiratory symptoms; Lower respiratory symptoms; Cough; Nutritional status as measured by BMI; Glycemic control as measured by blood glucose level; Microbiological profile as measured by incidence of pseudomonas; Burden of care as measured by CFQ-R treatment burden domain score;		
SETTING:	Outpatient		
PERSPECTIVE:	Population		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE
PROBLEM	**Is the problem a priority?**	**Research evidence:**

	○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cystic fibrosis is an autosomal recessive disease affecting multiple organ systems. Disease-related morbidities lead to shortened life expectancy. Approximately 30,000 people in the US have been diagnosed with CF. The carrier rate in the United States ranges from 1/29 among Caucasian-Americans to 1/90 among Asian-Americans. The most common CFTR mutation that causes CF is F508del. Approximately 47% of CF patients are homozygous for F508del and another 40% are compound heterozygotes, with one F508del mutation and another CF causing mutation.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Research evidence:** One randomized controlled trial assessed treatment with lumacaftor and ivacaftor vs no treatment for persons with two copies of F508del mutation among persons 18 years or older (Boyle 2014).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	

Outcomes	№ of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no treatment	Risk difference with ivacaftor/lumacaftor combination drug
Any pulmonary exacerbation follow up: 8 weeks	262 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 0.63** (0.33 to 1.20)	Study population	
				200 per 1,000	**74 fewer per 1,000** (134 fewer to 40 more)
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID follow up: 8 weeks	206 (1 RCT)	⊕⊕◯◯ LOW[a c d]	-	The mean pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID was **0**	MD **5.59 higher** (3.24 higher to 7.94 higher)
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor	171 (1 RCT)	⊕⊕◯◯ LOW[a c e]	-	The mean quality of life as measured by CFQ-R respiratory domain score -	MD **16.21 higher** (13.05 higher to 19.38 higher)

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250 mg BID follow up: 8 weeks				ivacaftor 250 mg BID was **0**	
Any serious adverse event follow up: 8 weeks	262 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 0.59** (0.23 to 1.52)	Study population	
				107 per 1,000	**44 fewer per 1,000** (82 fewer to 55 more)
Upper respiratory symptoms follow up: 8 weeks	262 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 1.21** (0.82 to 1.79)	Study population	
				267 per 1,000	**56 more per 1,000** (48 fewer to 211 more)
Lower respiratory symptoms follow up: 8 weeks	262 (1 RCT)	⊕⊕◯◯ LOW[a b c]	**RR 1.11** (0.74 to 1.66)	Study population	
				320 per 1,000	**35 more per 1,000** (83 fewer to 211 more)
Nutritional status as measured by BMI - not reported	-	-	-	-	-

a. Boyle 2014 control counted multiple times.
b. 95% CI crosses line of no effect.
c. Control group includes both F508del homozygous (n~17) and heterozygous (n~6). Mean FEV1 reported 68.5% (range: 38.3-101.7).
d. I2 = 96%.
e. I2 = 88%.

Additional considerations:

Pulmonary function and QoL are increased based on the results from this trial.

Additional potential harms include cataracts and the need for frequent monitoring, as well as other drug interaction (e.g., hormonal contraceptives). There is uncertainty about long-term harms of treatment.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**Additional considerations:** The panel agreed that serious indirectness exists based on the FEV1 level of the included population.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research evidence:** No research evidence identified. **Additional considerations:** Parents and patients with CF might value the therapy less when they have a high lung function, particularly because we don't know the long term side effects. There are follow-up and additional tests that would be needed when on this therapy, which might lead to greater variability about the potential benefits of the treatment.
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Additional considerations:** Based on the certainty in the evidence, the panel has some uncertainty about the balance of benefits and harms.

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RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Research evidence:** Ivacaftor/lumacaftor list price as of 2015: $259,000 per year (based on media sources). Actual cost to insurers might be less based on negotiations with insurers and pharmacy benefit managers. Generally, both drugs are covered among private insurers and public programs (Medicaid, Medicare, etc.) in the US. However, some insurers have placed restrictions on which patients can receive the drug. For example, a handful of state Medicaid programs have limited access to people with CF who have lung function values between 40-90%. Thus people outside of this range may not be able to get the drug. Other limiting criteria are issues such as having the indicated genotype, proof of improvement or maintenance of BMI and/or FEV1 while on drug, no presence of certain bacterial species, adherence with therapy and/or possible drug-drug interactions with other CF medications, etc.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ● High ○ No included studies	**Research evidence:** The ivacaftor/lumacaftor list price is available in the public domain.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies	**Research evidence:** One cost-effectiveness analysis for the National Health Service in the UK modeled three scenarios for the use of ivacaftor among persons aged 12 years and older, 40-90% FEV1 at baseline with CF who are homozygous for F508del mutation. This health technology assessment used findings from TRANSPORT, TRAFFIC, and PROGRESS. The incremental cost-effectiveness ratio (ICER) for lumacaftor–ivacaftor plus standard of care compared with standard of care alone ranged from £135,500 to £459,000 per quality-adjusted life year (QALY) gained. Model assumptions: FEV1 increased by 2.8% at 16 weeks and was maintained among persons on treatment to reflect TRANSPORT and TRAFFIC. After week 24 in the model, ppFEV1 declined for people having standard of care alone and for people having lumacaftor–ivacaftor plus standard of care. The decline in ppFEV1 was age dependent for standard of care alone based on a large US and Canadian observational study of 4,161 adults and 1,359 children.

	○ No included studies	Model included: antibiotics for pulmonary exacerbation, hospitalizations, 24.7% required lung transplant (of those less than 30% FEV1), discount rate of 3.5%, and treatment adherence of 90%. **Additional considerations:** The panel discussed the results from the NHS report and decided that the results are too indirect to consider for this recommendation. While the panel recognizes that patients with low FEV1 may respond more homogenously, persons with CF may be at risk for more costs if no treatment or accrue more costs from other treatments, transplants, or other services.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** A recommendation for treatment might increase equity for patients to receive ivacaftor/lumacaftor; however, if patients are ineligible for treatment then they might be disadvantaged. In addition, health coverage is variable by state.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Research evidence:** One study assessed barriers to adherence to ivacaftor by using a self-report survey. Two patients identified barriers to adherence, which were "insurance does not cover my medication" and "I do not like how the medication makes me feel." The most common reason for not adhering to ivacaftor following discussion of the individual adherence results was "I forgot to take it" (Siracusa et al., 2015). **Additional considerations:** The panel listed the following as potential stakeholders for this recommendation: people with CF, parents/care givers of people with CF, healthcare providers, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies. While people with CF, parents/care givers of people with CF, and healthcare providers would find the intervention acceptable, payers, pharmaceutical companies, health systems, hospitals, and specialty pharmacies may either not find the treatment acceptable or have variable opinions of acceptability.

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FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Research evidence:** No research evidence identified. **Additional considerations:** The panel agreed that this treatment would probably be feasible to implement, given their current experience in practice. More information is needed on the sustainability of the treatment; however, they did not identify barriers that would limit feasibility such as clinical staff, clinical expertise, ease of prescribing or obtaining prior authorization, care-taker effort or burden of care.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
			intervention or the comparison					
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	**High**			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation?

TYPE OF RECOMMENDATION	Strong recommendation	Conditional recommendation	Conditional recommendation for either the	Conditional recommendation	Strong recommendation

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	against the intervention ○	against the intervention ○	intervention or the comparison ○	for the intervention ●	for the intervention ○
RECOMMENDATION	CFTR modulator guideline panel suggests ivacaftor/lumacaftor combination drug vs. no treatment be used in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation**.** *Conditional recommendation, Low certainty in the evidence* Remarks: -ivacaftor/lumacaftor suggest benefit; however, there are unknown long-term harms. -ivacaftor/lumacaftor may provide benefit for patients who are symptomatic or lower FEV1 level -Cost needs to be considered				
JUSTIFICATION	This recommendation places a high value on the potential improvement of patient-important outcomes such as lung function as assessed by PPFEV1 and less value on the substantial expected costs of the therapy. The committee acknowledged very indirect evidence for the benefit of treatment with IVA/LUM for patients age 18 years and older with PPFEV1 > 90%. This resulted in low certainty regarding benefits and a conditional recommendation. Additional factors in this decision included cost/benefit considerations and potential issues with drug-drug interaction, birth control, and possible long term adverse effects (liver disease). Another important discussion point was whether an adult population with normal lung function would desire initiation of a very costly therapy, particularly in light of possible complicating issues as just described. A decision to start therapy would clearly require discussion between patient and provider. Thus, the committee elected to suggest rather than recommend treatment. The high cost of the medication may limit the acceptability of this therapy to key stakeholders especially payers and capitated closed health systems. Two panel members were absent during the discussion and recommendation.				
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS	Predominant implementation considerations include discussions with the patients or care givers about healthcare coverage. The panel identified health insurance and coverage of CFTR modulators as the main barrier to implementation. Healthcare costs and coverage (including treatment costs) are variable.				

MONITORING AND EVALUATION	For persons with CF who receive ivacaftor/lumacaftor, regular monitoring should include LFTs, cataracts development in kids, adherence to treatment, SAEs or AEs, and sweat chloride. However, sweat chloride monitoring change with use of ivacaftor might not be informative for M&E.
RESEARCH PRIORITIES	Future research is needed in the form of a clinical trial to evaluate age group and FEV1 status of interest. A post-market efficacy trial would inform implementation at the population level by capturing information on tolerability of the treatment, adherence, and efficacy. Cost-effectiveness research is needed to inform coverage decisions. For patients with healthier lung functions, additional research should evaluate methods for preservation of lung function.

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Evidence Profile for Recommendation 30

Ivacaftor/lumacaftor combination drug compared to no treatment in individuals age 18 and older and FEV1 greater than 90% predicted with a diagnosis of CF and two copies of the F508del mutation

Setting: Outpatient

Bibliography: Boyle, M. P., Bell, S. C., Konstan, M. W., McColley, S. A., Rowe, S. M., Rietschel, E., ... & VX09-809-102 study group. (2014). 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 randomized controlled trial. The Lancet Respiratory Medicine, 2(7), 527-538.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Any pulmonary exacerbation (follow up: 8 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	12/112 (10.7%)	30/150 (20.0%)	**RR 0.63** (0.33 to 1.20)	**74 fewer per 1,000** (from 40 more to 134 fewer)	⊕⊕◯◯ LOW	CRITICAL
Pulmonary function as measured by absolute change in percent predicted FEV1 - ivacaftor 250 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	serious [a,d]	serious [b]	not serious	none	89	117	-	MD **5.59 higher** (3.24 higher to 7.94 higher)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
Quality of life as measured by CFQ-R respiratory domain score - ivacaftor 250 mg BID (follow up: 8 weeks)												
1	randomized trials	not serious	serious [a,e]	serious [b]	not serious	none	71	100	-	MD **16.21 higher** (13.05 higher to 19.38 higher)	⊕⊕◯◯ LOW	CRITICAL
Any serious adverse event (follow up: 8 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	5/112 (4.5%)	16/150 (10.7%)	**RR 0.59** (0.23 to 1.52)	**44 fewer per 1,000** (from 55 more to 82 fewer)	⊕⊕◯◯ LOW	CRITICAL
Upper respiratory symptoms (follow up: 8 weeks)												
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	33/112 (29.5%)	40/150 (26.7%)	**RR 1.21** (0.82 to 1.79)	**56 more per 1,000** (from 48 fewer to 211 more)	⊕⊕◯◯ LOW	CRITICAL
Lower respiratory symptoms (follow up: 8 weeks)												

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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ivacaftor/lumacaftor combination drug	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious [a]	serious [b]	serious [c]	none	34/112 (30.4%)	48/150 (32.0%)	**RR 1.11** (0.74 to 1.66)	**35 more per 1,000** (from 83 fewer to 211 more)	⨁⨁◯◯ LOW	CRITICAL
Nutritional status as measured by BMI - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

a. Boyle 2014 control counted multiple times in the analysis.

b. Control group includes both F508del homozygous (n~17) and heterozygous (n~6). Mean FEV1 reported 68.5% (range: 38.3-101.7).

c. 95% CI crosses line of no effect.

d. I2 = 96%.

e. I2 = 88%.

References of Cited Studies

Boyle, M. P., Bell, S. C., Konstan, M. W., McColley, S. A., Rowe, S. M., Rietschel, E., ... & VX09-809-102 study group. (2014). 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 randomized controlled trial. The Lancet Respiratory Medicine, 2(7), 527-538.

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