Summary

WHAT IS CYSTIC FIBROSIS?

Cystic fibrosis (CF) is a progressive genetic disease that affects many organ systems, though a significant proportion of its morbidity and mortality is associated with its impacts on the lungs. In 2016, an estimated 30,000 individuals in the US were living with CF.

CF is linked to mutations in the CF transmembrane conductance regulator (*CFTR*) gene. While there are over 300 genetic mutations known to be associated with CF, the *F508del* mutation is most common, affecting 86% of patients. About half of those who have the *F508del* mutation have two copies with the mutation (homozygous), and the other half have one copy with *F508del* and a copy with another mutation (heterozygous).

TREATMENT OPTIONS

ICER's report updated our review on three existing CFTR modulator drugs:

- **Ivacaftor (Kalydeco®)**
- **Lumacaftor/ivacaftor (Orkambi®)**
- **Tezacaftor/ivacaftor (Symdeko®)**

And evaluated one new therapy just approved by the FDA:

- **Elexacaftor/tezacaftor/ivacaftor (Trikafta®)**

Kalydeco, Orkambi, and Symdeko, fall under ICER's framework for therapies for ultra-rare diseases; Trikafta did not fall under the ultra-rare disease framework because it is intended for use in a patient population larger than 10,000 individuals. 90% of individuals with CF have a mutation amenable to treatment with Trikafta.

This analysis examined the impact of these drugs (as relevant) in the following four populations:

- **Population 1:** Individuals with CF mutations with FDA indications for Kalydeco
- **Population 2:** Individuals with CF homozygous for the *F508del* mutation
- **Population 3:** Individuals with CF heterozygous for the *F508del* mutation and a residual function mutation (the second copy of the gene makes some working protein
- **Population 4:** Individuals with CF heterozygous for the *F508del* mutation and a minimal function mutation (the second copy of the gene makes little or no working protein)

KEY REPORT FINDINGS

- **For population 2**, evidence on Trikafta provides high confidence of a substantial net health benefit when compared with best supportive care alone.
- **For population 2**, evidence on Trikfafta provides high confidence of a substantial net health benefit when compared with Symdeko.
- **For population 3**, there was moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit for Trikafta compared to Symdeko.
- **For population 4**, Trikafta provides high confidence of a substantial net health benefit compared with best supportive care.
- Additional benefits accrue for family members, caregivers, and society.
- For all four CFTR modulators, analyses suggest that the prices set by the manufacturer would need to be deeply discounted to align fairly with these benefits.

KEY POLICY RECOMMENDATIONS

- The manufacturer should lower Trikafta's price to fairly align with its demonstrated benefits. Fair prices reward innovation and improve patient access, while excessive pricing causes harm to individuals with CF as well as individuals with other conditions who may have no choice but to delay or forego care, or drop their health insurance.
- Public and private payers should continue to affirm their commitment to provide access to the CFTR modulators and should remove superfluous requirements for coverage approval and continuation.
- Future studies should measure and report a broad set of outcomes to better assess the health and economic impact of CF interventions to patients, their caregivers, and their health system. The CF Foundation is currently conducting several such studies and should be commended for these efforts.

Clinical Analyses

How strong is the evidence that these therapies improve outcomes in patients with cystic fibrosis?

ICER EVIDENCE RATINGS

Intervention*	ICER Evidence Rating
Population 1: Eligible for Kalydeco	
Kalydeco vs. BSC	A
Population 2: Homozygous *F508del*	
Orkambi vs. BSC	B
Symdeko vs. BSC	B+
Trikafta vs. BSC	A
Trikafta vs. Symdeko	A
Population 3: Heterozygous *F508del* / Residual Function Mutation	
Symdeko vs. BSC	B+
Trikafta vs. BSC	B+
Trikafta vs. Symdeko	C++
Population 4: Heterozygous *F508del* / Minimal Function Mutation	
Trikafta vs. BSC	A

BSC: best supportive care
*All interventions are in addition to BSC
Evidence ratings weighed uncertainties about potential harms of the treatments against the benefits.

- Trikafta earned ICER's highest "A" evidence rating for the indicated populations where published clinical data exist; the evidence provides high certainty that Trikafta provides a substantial net health benefit over standard care and over Symdeko.

- Although data on Trikafta have not yet been published in patients who are heterozygous for the *F508del* mutation and a residual function mutation, ICER determined that using Trikafta to treat that sub-population is likely to be at least as good as treating with Symdeko, and possibly better (C++).

- For the other three related treatments – Symdeko, Orkambi, and Kalydeco – ICER's evaluation of new evidence since our 2018 assessment confirms our previous evidence ratings. For their respective indicated populations, and compared to best supportive care, the evidence provides high certainty that Kalydeco provides a substantial net health benefit, Orkambi provides a small net health benefit, and Symdeko provides at least a small net health benefit with the potential for a substantial benefit.

Clinical Analyses (continued)

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

Key Outcomes:

- $ppFEV_1$: Percent predicted forced expiratory volume in 1 second
- Pulmonary exacerbations
- Respiratory Symptom Scale of the Cystic Fibrosis Questionnaire - Revised (CFQ-R)

	Absolute $ppFEV_1$	Pulmonary Exacerbations	Respiratory Symptom Scale and Quality of Life (CFQ-R)
Population 1: Individuals with CF Who Carry Mutations Included in the FDA-Approved Indications for Kalydeco			
Kalydeco	↑ Important improvement	↓ Large reduction (except in those with *R117h* mutation)	↑ Important improvement
Population 2: Individuals with CF Who Are Homozygous for the *F508del* Mutation			
Orkambi	↑ Modest improvement	↓ Large reduction	↑ Small improvement
Symdeko	↑ Modest improvement	↓ Large reduction	↑ Important improvement
Trikafta v. Symdeko	↑ Important improvement	↓ Large reduction	↑ Important improvement
Population 3: Individuals with CF Who Are Heterozygous for the *F508del* Mutation with a Residual Function Mutation			
Kalydeco	↑ Important improvement	No significant differences reported	↑ Important improvement
Symdeko	↑ Important improvement	No significant differences reported; exploratory endpoints	↑ Important improvement
Trikafta	No published data available for treatment with Trikafta in this population		
Population 4: Individuals with CF Who Are Heterozygous for the *F508del* Mutation with a Minimal Function Mutation			
Trikafta	↑ Important improvement	↓ Large reduction	↑ Important improvement

Clinical Analyses (continued)

HARMS

For all three CFTR modulators approved prior to Trikafta, harms were mild and generally uncommon. For Trikafta, there is no evidence of significant harms.

SOURCES OF UNCERTAINTY

Patient important outcomes: ppFEV$_1$ is a surrogate measure of CF disease severity. Despite its wide use as the primary outcome in clinical trials and clinical practice, both the absolute ppFEV$_1$ level and changes in ppFEV$_1$ cannot fully capture disease severity or the clinical impact of modulator therapy on the many organ systems impacted by CF and the life experiences of patients.

Minimal long-term data for new therapies: CF is a chronic disease that impacts patients every day of their lives. The two pivotal clinical trials of Trikafta lasted 4 and 24 weeks respectively, which is not long enough to provide stable estimates for the long-term impact of Trikafta. In addition, there are likely differences in the long-term benefits of Trikafta based on the age of the patient when therapy is initiated and the severity of CF symptoms at initiation. Finally, in patients heterozygous for the *F508del* mutation and a residual function mutation, there are no data on Trikafta, though we do have data on Symdeko, which includes two of the 3 drugs in Trikafta.

Generalizability of Trial Results: CF genetics are highly complex and variable, and the populations with any one type of heterozygous *F508del* plus another mutation are relatively small.

Access to Care: Many trials were conducted in accredited CF specialty centers. It is uncertain whether gains in survival are distributed unequally due to differences in access to CF care centers in the US.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

Treatment vs. BSC	Cost Per QALY Gained	Cost Per evLYG
Population 1: Eligible for Kalydeco Monotherapy Only		
Kalydeco Plus BSC	$1,370,000	$1,180,000
Population 2: Homozygous for the *F508del* Mutation		
Orkambi Plus BSC	$1,480,000	$1,360,000
Symdeko Plus BSC	$1,380,000	$1,200,000
Trikafta Plus BSC	$1,160,000	$1,040,000
Population 3: Heterozygous *F508del* with a Residual Function Mutation		
Symdeko Plus BSC	$1,340,000	$1,100,000
Trikafta Plus BSC	$1,100,000	$951,000
Population 4: Heterozygous *F508del* with a Minimal Function Mutation		
Trikafta Plus BSC	$1,050,000	$877,000

For all CFTR modulators in all CF populations evaluated, the number of iterations in which the CFTR modulators were cost-effective at a threshold of $500,000 per QALY or lower (or $200,000 per QALY or lower for Trikafta) was approximately 0%.

Economic Analyses (continued)

HEALTH-BENEFIT PRICE BENCHMARKS

What is a fair price for these therapies based on its value to patients and the health care system?

	Annual WAC	Annual Price to Achieve $100,000 - $150,000/QALY Threshold based on Assumed Price	Change from Assumed WAC Required to Reach Threshold Prices	Assumed Price within or below range?
Kalydeco	$311,704	$58,600-$68,600	78% to 81%	NO
Orkambi	$272,623	$50,800-$58,900	78% to 81%	NO
Symdeko	$292,200	$56,200-$65,500	78% to 81%	NO
Trikafta	$311,741	$67,900-$79,900	74% to 78%	NO

ICER's recommended health-benefit price benchmark (HBPB) for Trikafta is $67,900-$79,900 per year, which would require at least a 74% discount off the treatment's current list price.

The HBPB is a price range suggesting the highest US price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients in the health system due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

51% of patients in population 2 and 10% of patients in population 3 could be treated with Trikafta without exceeding the $819 million ICER potential budget impact threshold at list price. However, for Population 4, only approximately 90% of patients could be treated before exceeding the potential budget impact threshold at this price.

When combined for all populations, the annualized potential budget impact of treating the entire eligible population with Trikafta at list price would exceed the potential budget impact threshold by 71%.

ICER is issuing an Access and Affordability Alert for Trikafta. Throughout ICER's review, clinical expert input suggested that all eligible patients receive a CFTR modulator, with Trikafta being the preferred choice for most patients. Assuming all eligible patients who are already on an older CFTR modulator transitioned to Trikafta, only 35% of newly eligible patients could be treated with Trikafta at its current list price before crossing ICER's potential budget impact threshold of $819 million per year.

The purpose of an ICER Access and Affordability Alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

Voting Results

The CTAF deliberated on key questions raised by ICER's report at a public meeting on August 27, 2020. The results of the votes are presented below. More detail on the voting is provided in the full report.

CLINICAL EVIDENCE

Population 2: Individuals with CF homozygous for the *F508del* mutation

- All panelists found the evidence was adequate to demonstrate a net health benefit of Trikafta and best supportive care compared to best supportive care alone.
- All panelists found the evidence was adequate to demonstrate a greater net health benefit with Trikafta and best supportive care compared to Symdeko and best supportive care.

Population 3: Individuals with CF heterozygous for the *F508del* mutation and a residual function mutation

- A majority of panelists found the evidence was adequate to demonstrate a net health benefit of Trikafta and best supportive care compared to best supportive care alone.
- A slight majority of panelists found the evidence was inadequate to demonstrate a greater net health benefit with Trikafta and best supportive care compared to Symdeko and best supportive care.

Population 4: Individuals with CF heterozygous for the *F508del* mutation and a minimal function mutation

- All panelists found the evidence was adequate to demonstrate a net health benefit of Trikafta and best supportive care compared to best supportive care alone.

POTENTIAL OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of panelists found when comparing Trikafta to best supportive care, Trikafta will significantly reduce the impacts of CF on family and caregivers.
- For population 4, a majority of panelists found when comparing Trikafta to best supportive care, Trikafta offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
- A majority also found that Trikafta has a significant impact on improving patients' ability to return to work and/or overall productivity.
- A majority of panelists found that Trikafta will have a significant positive impact outside the family, including on schools and/or communities.
- Six panelists acknowledged Trikafta could bring additional benefits including reducing the need for lung transplants in CF patients, which could make them available for other indications.
- All panelists found that Trikafta is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
- All panelists found that Trikafta is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
- A majority of panelists found that there is significant uncertainty about the magnitude or durability of long-term benefits of Trikafta. Similarly, a majority of panelists found significant uncertainty about the long-term risk of serious side effects.

Policy Recommendations

For Payers

- Public and private payers should continue to affirm their commitment to provide access to the CFTR modulators and should remove superfluous requirements for coverage approval and continuation.

For Providers

- Professional societies should highlight the impact on their patients of failed pricing and insurance policies and demand to be part of a public process to guide pricing and access decisions while ensuring future innovation.

For Manufacturers

- The manufacturer should lower Trikafta's price to fairly align with its demonstrated benefits. Fair prices reward innovation and improve patient access, while excessive pricing causes harm to individuals with CF as well as individuals with other conditions who may have no choice but to delay or forego care, or drop their health insurance.

- The manufacturer, which has a monopoly on CFTR modulators, bears significant social responsibility to exercise restraint when pricing its therapies and should participate in public deliberations.

For Clinical Researchers

- Future studies should measure and report a broad set of outcomes to better assess the health and economic impact of CF interventions to patients, their caregivers, and their health system. The CF Foundation is currently conducting several such studies and should be commended for these efforts.

- Large studies with long term follow-up are needed to complement the short-term results observed in the pivotal randomized trials.

- Patients who are heterozygous of the *F508del* mutation and a residual function mutation should be prioritized in future research

For Patient Organizations

- Patient organizations with a leading role in funding, organizing, and promoting innovative research into new treatments should demand commitments from manufacturers for sustainable pricing.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer-review.org).