Modulator Treatments for Cystic Fibrosis: Final Policy Recommendations

September 23, 2020

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the August 27, 2020 California Technology Assessment Forum (CTAF) public meeting on the use of Trikafta for the treatment of cystic fibrosis patients with at least one *F508del* mutation. At the meeting, ICER presented the findings of its revised report on Trikafta (although other CFTR modulators were included in the assessment, the meeting focused on Trikafta) and the CTAF voting council deliberated on key questions related to its comparative clinical effectiveness and associated potential other benefits and contextual considerations. Following the votes, ICER convened a Policy Roundtable of one patient with CF, one family member of an individual with CF, a representative from a patient advocacy organization, two practicing CF clinical experts, and two payer representatives to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. Much of the policy roundtable discussion centered on the impact that the high costs for CFTR modulators, and Trikafta in particular, on coverage policy. The ensuing discussion allowed a deeper exploration of the perspectives of patients and their families, of CF advocacy groups, and of public and private insurers wrestling with these challenges.

The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

1. ***The manufacturer should lower the price of Trikafta to align fairly with its demonstrated benefits. Pricing treatments within a proportional level to their benefits allows a health system to reward innovation and improve access to patients. Pricing far beyond this reasonable level causes harm to patients – some with CF and some with other diseases – who are forced to delay or forego care or even to drop health insurance entirely.***

Trikafta represents a major clinical advance for the care of CF and provides superior benefits compared to other modulators. However, our report's findings and discussion at the public meeting indicate that its price set too high in relation to its clinical benefits. When treatments are priced too high, they contribute to higher insurance premiums, copayments, and restrictions on access. Studies have shown that as insurance costs increase patients may delay care, forego care entirely, or even drop their health insurance. This leads to increased suffering and mortality. We heard stories of CF patients in these exact circumstances in the public comments on our draft report.

Despite this disconnect, we are confident that no insurer in the United States will even briefly entertain the option of non-covering Trikafta. The experience with our last report may serve as a reassurance. To our knowledge no insurer, including New York Medicaid, who used our report as part of their identification of a price target for negotiation over the price of Orkambi, even whispered about possible non-coverage. In fact, New York Medicaid made explicit that in no way would its negotiation include any possibility of erecting increased barriers to access in any way. We too, at our first public meeting on CFTR modulators, started by asserting that payers will cover these drugs (see video, 20:00-21:00).

To be entirely clear, in all cases we support actions to achieve fair prices that maintain the ability of patients to get the treatments they will benefit from. When we as a nation give a company a monopoly on a treatment and, instead of "wrestling" with them over coverage, tacitly agree that coverage will be provided because we want all patients to benefit, we need some mechanism to suggest an upper limit to the price that a company feels it can charge. It is precisely because access to Trikafta is not and should not be viewed as negotiable that we believe it is essential to use evidence of how much its benefits patients as a guide for its price. When the price of any service throughout the health system is way out of proportion to its ability to improve lives, it can cause more harm to other patients -- some with CF, some with other diseases – who can no longer afford their health care.

2. ***Benefiting from monopoly pricing power, the manufacturer of Trikafta and the other available CFTR modulators bears a significant social responsibility to change its pricing approach by exercising restraint in the use of its monopoly pricing power and by committing to engaging in public deliberations in which independent evaluations of the evidence will be discussed and integrated with broader considerations of value through input from patients and other key stakeholders.***

The first CFTR modulator was approved eight years ago, so changes to the treatment pathway and adjustments to clinical practice are therefore reasonably mature. The manufacturer should no longer make vague justifications for the high prices of the CFTR modulators based on general statements about research and development costs or prospects for future innovation and continued investment in new treatments for CF. These arguments increasingly ring hollow in the absence of any quantification or further details to contextualize them. The manufacturer bears further responsibility to change their approach to justifying their pricing during a phase when they have enjoyed sustained company growth, rising profits and stock values, and have funded substantial stock repurchase programs. In addition, any benefit of the doubt given by payers when Kalydeco was first approved for a small subset of the CF population has vanished with the introduction of newer treatments for much larger groups of patients. The manufacturer should therefore be fully transparent about the calculus made for pricing of the CFTR modulators and be willing to engage in processes intended to produce independent judgments of what fair pricing and sustainable access look like for CF innovations.

Finally, the manufacturer no longer can point to a small patient population in an orphan disease as the reason for exorbitant pricing. More than 27,000 patients are potentially eligible for Trikafta in the US alone. The company reported net revenue of $1.8 billion from Trikafta alone during the first 6 months of 2020 – it classifies as a blockbuster drug. The annual price for Trikafta is far above that of other drugs with a modest number of potentially eligible patients.

Payers

3. ***Prior authorization criteria for Trikafta should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.***

Coverage Criteria Considerations: Trikafta

1) **Diagnosis:**
   a) Proof of CFTR mutation status (at least one *F508del* mutation) should be required for initial coverage, but not for requalification as CFTR modulator treatments do not permanently

modify the genome.

2) **Clinical Eligibility Criteria:**
   a) 12 years of age or older is the age threshold supported by direct clinical evidence and codified at the time Trikafta was first approved by the FDA. Given that there is no *a priori* clinical rationale that younger patients would not benefit, and that more recent evidence suggests that the FDA may soon expand the label to a younger population, payers should establish clear pathways for exceptions and consider coverage for younger patients meeting other clinical criteria. It is reasonable for payers to require these exception requests be made by a practicing CF expert, as the potential side effects of using the approved dose in a pediatric population are not yet known.

   b) Baseline ppFEV1 level should not be a consideration for coverage. Clinical experts indicated that, although trials excluded patients with ppFEV1 <40% and >90%, there is no clinical reason to suspect that patients outside of these ranges would not have comparable risks and benefits to those of the study population.

   c) It is reasonable for insurers to require physician attestation that the patient is receiving best supportive care.

   d) Sweat chloride levels should not be used for eligibility or renewal criteria, as expert opinion indicated that it is not predictive of clinical response.

   e) Patients who have had a liver transplant should not be excluded from coverage. Although these patients were excluded from the clinical trial, expert input indicated that they are still likely to receive benefit from Trikafta.

3) **Concomitant use of other therapies**: There is no evidence to support combination therapy with another currently-available CFTR modulator treatment (Kalydeco, Symdeko, or Orkambi).

4) **Step Therapy:** In general step therapy should not be required for patients who qualify for Trikafta because Trikafta is clearly superior to Symdeko and Orkambi in most patients who carry the *F508del* mutation. It may be clinically reasonable to consider Symdeko in patients heterozygous for *F508del* with a residual function mutation if Symdeko becomes much less expensive, although insurers should be prepared to rapidly update these policies once data on the effectiveness of Trikafta in this population become available.

5) **Renewal Criteria:**
   a) Provider attestation of clinical benefit is sufficient given that there is no defined standard for clinical response to treatment. Clinical expert input indicated that modulator therapy may improve, maintain, or slow the decline of respiratory function, which all represent important health benefits for CF patients.

b) Repeat genetic testing should not be required for renewal, as CFTR modulator treatments do not permanently modify the genome.

6) **Provider Criteria:** Given the complexity of managing CF and of ensuring appropriate overall care for patients, it is reasonable for insurers to require that Trikafta be prescribed by a CF clinical expert.

4. 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 the CFTR drugs, it is important for payers to seek to control costs without using access restrictions as a key feature of negotiation. Patients and their families need to know that insurers will help them receive these new drugs. Testimony provided at the policy roundtable highlighted that most payers have dropped unnecessary, and at times illogical, requirements for documentation prior to approval of insurance coverage for both Kalydeco and Trikafta. Two examples were the removal of requirements for periodic genetic testing and requirements that supportive care fail patients before they can access modulator treatment. However, some barriers remain, such as step therapy protocols that require patients eligible for Trikafta to try Symdeko or Orkambi first. Discussion at the meeting indicated that such barriers are less prevalent for highly-effective modulator therapies like Kalydeco and Trikafta, and more prevalent for other supportive treatments for CF. One roundtable participant praised the many public and private insurers who provided access to Trikafta through case-by-case decisions before it was added to their formularies, noting that this type of response to an early approval by the FDA reflected the strength of the clinical evidence and was beneficial for individuals with CF.

A CF patient expert on the roundtable noted that many individuals with CF have difficulty finding their insurer's coverage policy for Trikafta, an issue that is suspected to be more common among smaller regional insurers. It is essential that all insurers make their coverage criteria readily available and that policies are clearly written.

Patient Advocacy Organizations

5. Patient organizations that have a leading role in funding, organizing, promoting, and otherwise fostering innovative research on new treatments should demand commitments from manufacturers for sustainable pricing of the products patients helped bring to the market.

It is likely that without the CF Foundation's efforts, the drug developers would have prioritized other diseases and the innovations that resulted in CFTR modulator therapies may not have been

realized. However, the CF Foundation has not had a "seat at the table" to discuss the pricing of these innovations. While other patient organizations should hold the CF Foundation up as an example of how to fund research and development in an underserved area, they must also couple this with a requirement of the developers to commit to sustainable pricing practices.

Specialty Societies

6. ***Professional societies should fully exercise their responsibility by bearing witness to the impact on their patients of failed pricing and insurance policies and by demanding to be part of the public process that should guide pricing to balance the needs for affordability and for investments in future innovation.***

There is considerable excitement in the clinical community about the potential for both short-term and sustained clinical benefit with the CFTR modulators, but physicians also have a front-row seat to the inequities and access challenges posed by the pricing of these drugs. The oncology community is an important model for physician activism, having highlighted the financial toxicity associated with new cancer regimens. The CF clinical community should consider a similar effort, given the financial challenges posed by CFTR modulators and other supportive-care treatments for CF.

Researchers

7. ***Leading journals should refuse to publish manuscripts based on clinical trials that redact portions of their trial protocols.***

The protocol for the pivotal trial of Trikafta in patients heterozygous for the *F508del* mutation was made available electronically with the publication of the results of the trial in the New England Journal of Medicine but it was heavily redacted, raising questions about the fidelity of the methods and results of the trial. Transparency is an essential component in randomized clinical trials. Clinicians, guideline committees, and patients depend on the integrity of those designing, performing, and reporting clinical trials. Concerns that this process was not always performed ethically have led to the requirement that clinical trials be registered in public, online databases, such as clinicaltrials.gov prior to the recruitment of trial participants. More recently, high impact journals have published the clinical trials protocol as supplement to the results of pivotal trials. Sharing study protocols makes the critical appraisal of the trial more robust including the assessment of selective reporting of trial results and identifying when the pre-specified primary outcome and analytic methods are changed.

8. ***The groundbreaking studies initiated and funded by the Cystic Fibrosis Foundation should be applauded and may serve as a model for other patient organizations seeking to generate evidence. 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 played a central role in fostering the development of CFTR modulators as well as convincing manufacturers of the benefits of investing in CF innovation. Part of their strength is the development of a registry that includes the majority of patients with CF in the United States. They continue to innovate through randomized trials like SIMPLIFY, which seeks to identify which therapies included in the current best standard care can be safely stopped for patients on Trikafta. However, ICER's review identified a paucity of evidence on patient-centered outcomes pertaining to extrapulmonary manifestations of the disease, including but not limited to: mental health and affect, quality of life beyond the respiratory domain, impact on the endocrine, gastrointestinal, and functional effects of CF; impact on caregivers, including quality of life, affect, and time costs; and information on costs, including out of pocket costs, informal caregiver time, and transportation costs. Patients, clinicians, insurers, and other stakeholders need this information to make fully-informed decisions about their treatment and to ensure that the health system is spending its limited resources wisely. At a minimum, the full CFQ-R should be reported and the EQ-5D should be measured and reported. Specifically, a CF core outcomes set (COS) should be developed and applied. A CF-specific COS is under development (see http://www.comet-initiative.org/studies/details/882; http://www.comet-initiative.org/studies/details/120) that is considering many of these measures.

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

The randomized trials of the CFTR modulators demonstrated a short-term improvement in $ppFEV_1$. However, the impact of the CFTR inhibitors on the rate of decline in $ppFEV_1$ with ongoing treatment remains uncertain. Need long term studies, particularly on the impact of Trikafta on the decline in $ppFEV_1$ over time, the incidence of CFRD, and the ability to drop some of the standard therapies used to maintain the health of patients with CF. We applaud the efforts of the CF Foundation-sponsored PROMISE study, which is enrolling patients on Trikafta for a cohort study, but encourage them to extend follow-up beyond the planned two years.

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

The population of patients homozygous for the *F508del* mutation and a residual function mutation vary significantly in their clinical manifestations and thus may have variable responses to CFTR

modulators like Trikafta. This population should be a priority for future research and should be encouraged to participate in studies like PROMISE.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the August 27, 2020 Public meeting of CTAF.

Table 1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Avery McKenna, BS, Research Assistant	ICER	*
David Rind, MD, MSc, Chief Medical Officer	ICER	*
Jeffrey A. Tice, MD, Professor of Medicine	University of California, San Francisco	*
Kael Wherry, PhD	University of Minnesota, School of Public Health	*
Karen M. Kuntz, ScD, Professor	University of Minnesota School of Public Health	*
Matt Seidner, BS, Program Director	ICER	*
Monica Frederick, BS, Program and Event Coordinator	ICER	*
Noemi Fluetsch, MPH, Research Assistant	ICER	*
Rick Chapman, PhD, MS, Director of Health Economics	ICER	*
Steven D. Pearson, MD, MSc, President	ICER	*

*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.

Table 2. CTAF Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
Ann Raldow, MD, MPH	Assistant Professor, Department of Radiation Oncology, University of California, Los Angeles	*
Brian O'Sullivan, MD	Professor of Pediatric Pulmonology, Geisel School of Medicine at Dartmouth College	*
Felicia Cohn, PhD	Bioethics Director, Kaiser Permanente, Orange County	*
Jeffrey Klingman, MD	Chief of Neurology, The Permanente Medical Group	*
Joy Melnikow, MD, MPH	Director of the Center for Healthcare Policy and Research and Professor of Family and Community Medicine, University of California, Davis	*
Kimberly Gregory, MD, MPH	Vice Chair, Women's Healthcare Quality and Performance Improvement, Cedars-Sinai Medical Center	*
Neal Kohatsu, MD, MPH, FACPM	Chief Health Strategist, Population Health Group, Center for Healthcare Policy and Research, University of California, Davis	*
Paul Heidenreich, MD, MS (Chair)	Professor and Vice-Chair for Quality, Stanford University	*

Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA	Clinical Professor of Medicine, University of California, San Francisco	*
Rena K. Fox, MD	Professor of Medicine, University of California, San Francisco	*
Richard Seiden, JD	Patient Advocate, Retired Partner, Foley & Lardner LLP	*
Rita Redberg, MD, MSc, FACC	Cardiologist and Professor of Medicine, and Director of Women's Cardiovascular Services, University of California, San Francisco	*
Robert Collyar	Patient Advocate	*
Sei Lee, MD	Associate Professor of Medicine, University of California San Francisco	*

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Carlos Milla, MD, Professor of Pediatrics, Pulmonology, Stanford University School of Medicine	Dr. Milla has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals, Proteostasis Inc., and Eloxx Pharma. He also receives advisory board honorarium from Vertex Pharmaceuticals.
Don Maurice Kreis, JD, MS, Parent of Individual with CF	No financial conflicts of interest to disclose.
Janet Zachary-Elkind, Deputy Director, NY State Department of Health, Office of Health Insurance Programs	Janet Zachary-Elkind is an employee of the NY State Department of Health (Medicaid).
Jeff White, PharmD, MS, Staff Vice President, Clinical Pharmacy Services, IngenioRX (Anthem)	Dr. White is an employee of IngenioRx (Anthem) and owns stock in Anthem.
Manu Jain, MD, MSc, Professor, Department of Medicine (Pulmonary and Critical Care); Department of Pediatrics, Northwestern University	Dr. Jain has received in excess of $5,000 in advisory fees and research funding from Vertex Pharmaceuticals. He is also on the Speaker's Bureau of Vertex Pharmaceuticals and Gilead Sciences
Mariah Hanley, JD, Individual with CF	No financial conflicts of interest to disclose.
Mary Dwight, Senior Vice President of Policy and Advocacy, Cystic Fibrosis Foundation	CFF has received charitable contributions and/or fees for service in excess of $5,000 from health care companies including Vertex Pharmaceuticals. CFF has the option to acquire equity interests >$10,000 from a pharmaceutical company unrelated to this report. CFF has entered into therapeutic development award agreements that may result in intellectual property and royalty rights from various pharmaceutical companies