Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Public Meeting – May 17, 2018

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Welcome and Introduction

- **Why are we here today?**
  - Cystic fibrosis has a profound effect on patients and families, and innovative treatments have made a significant difference in their lives, with additional innovation on the horizon

"…for those who battle CF, every day is filled with hours of respiratory therapy, countless pills, and often multiple injections, IVs, and hospitalizations. Every hospitalization is painful, isolating, frightening, and expensive."

-Siri Vaeth and Sue Landgraf, Cystic Fibrosis Research, Inc

"When I was diagnosed with cystic fibrosis in 1984 at the age of three years old, my parents were told that they should not expect me to live to see my twelfth birthday….We still have a long way to go and while CFTR modulators are not a perfect answer and do not work for all those suffering from CF, they are an important and valuable piece to allow us to live and thrive."

-Chad Riedy

Welcome and Introduction

- **Why are we here today?**

"Vertex is exploiting its monopoly to gouge patients and payers."

-- Juliana Keeping, Mother of CF patient aged 5

Vertex is generating profits from its current drugs, but its newer drugs should be even more profitable. CEO Jeffrey Leiden noted that Vertex now "has a nice problem of accumulating cash very rapidly." At the end of 2017 that nice problem translated to over $2 billion in cash, cash equivalents, and marketable securities.

-- Motley Fool

Negotiations came to a head this month when Vertex… pulled the trials because CEPS wanted an 80% discount to the biotech's latest offer on Orkambi. "If countries can't recognize the innovation that we can bring – and an 80% discount isn't recognizing innovation – then it is not a viable business option for our other medicines."

-- BioCentury

Welcome and Introduction

- **Why are we here today?**
  - New treatments raise important questions about appropriate use, and cost
  - Need for objective evaluation and public discussion of the evidence on effectiveness and value
  - **Goal**: Accelerate the transition to a sustainable health care system in which all patients are guaranteed access to innovative, high-value care

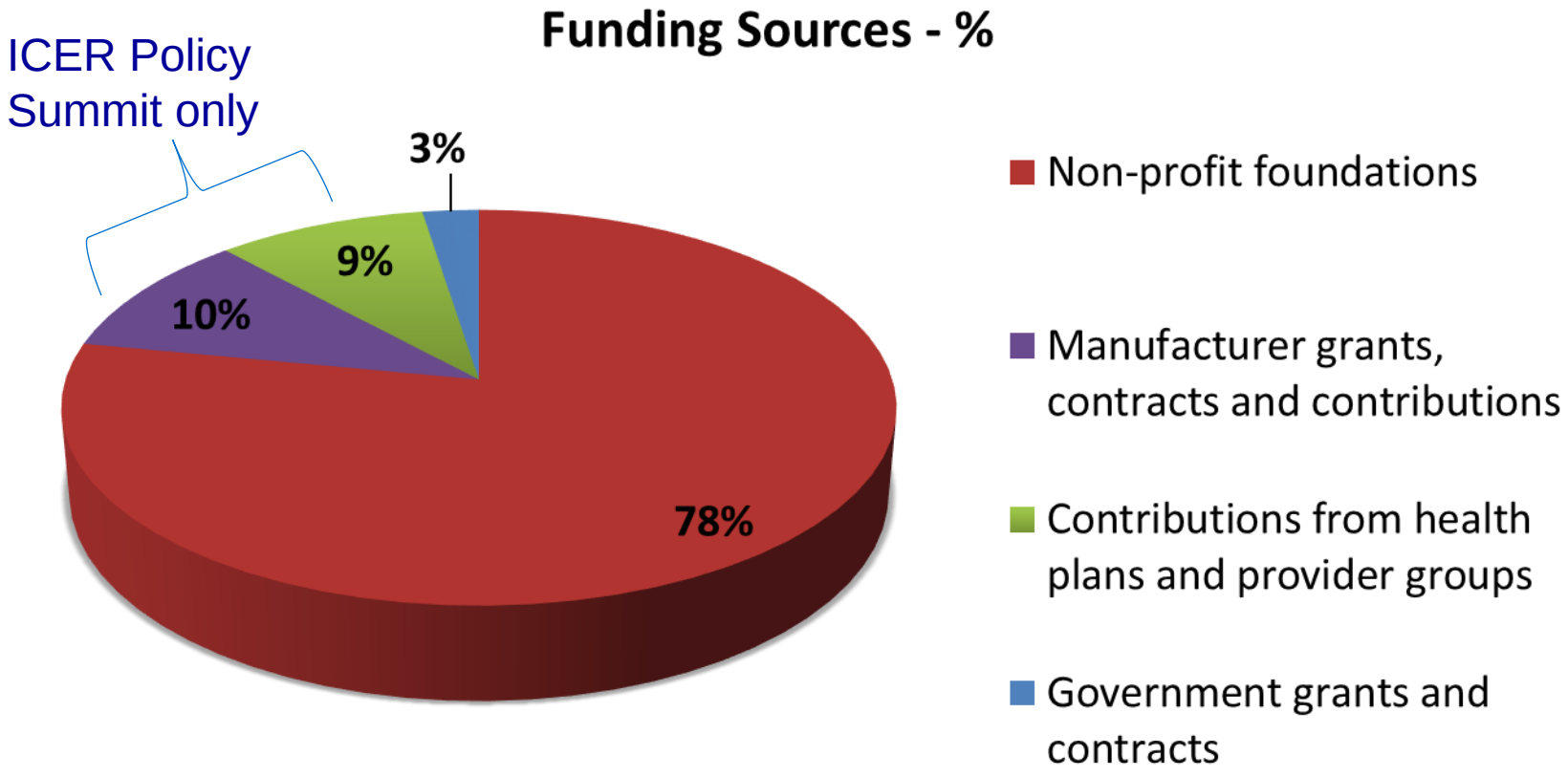
Welcome and Introduction

- Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

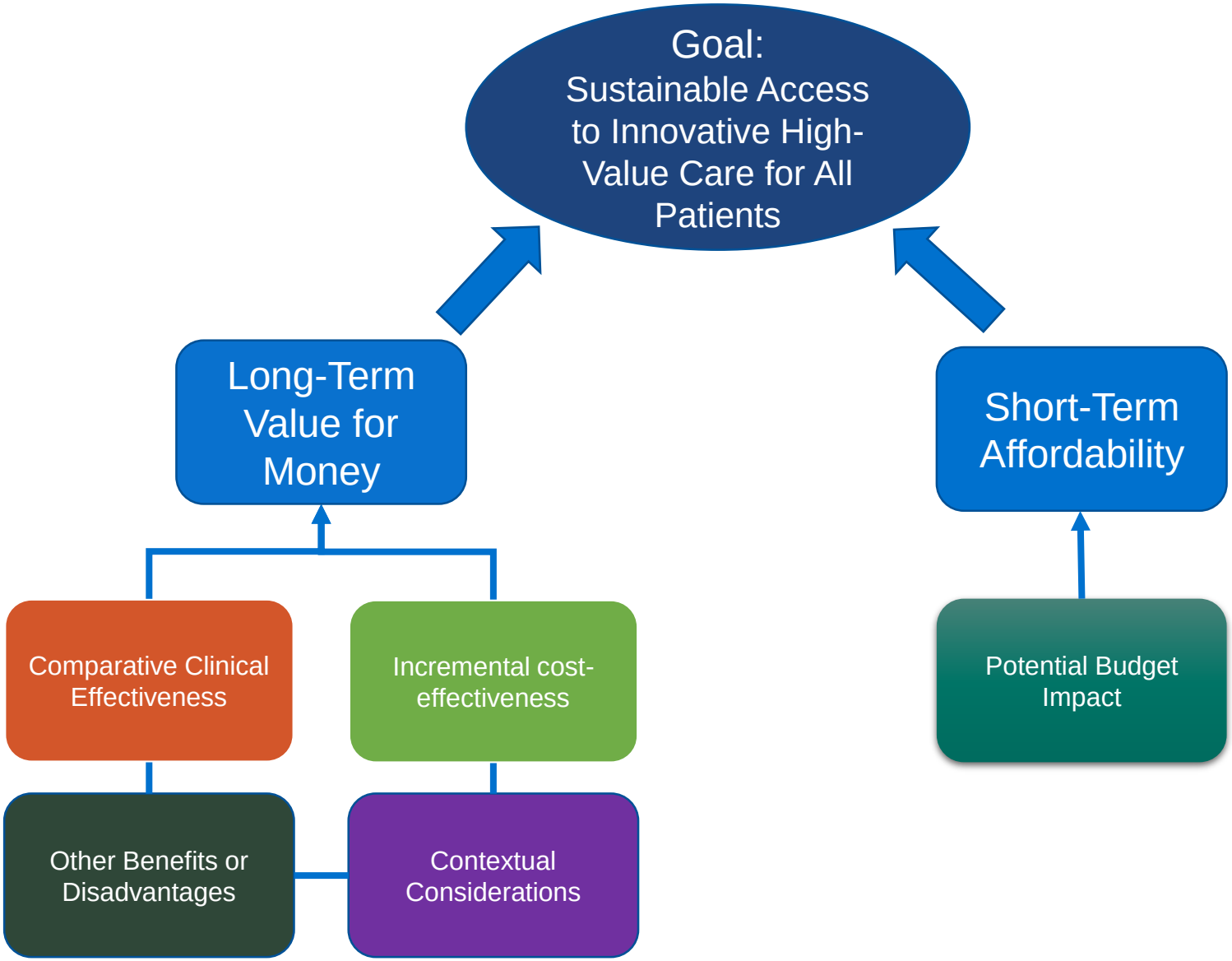
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on CFTR modulators for cystic fibrosis developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Evidence analysis by Brown University external consultants and ICER staff
- University of Minnesota cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Manu Jain, MD, MS
  - Brian O'Sullivan, MD
  - Cystic Fibrosis Foundation
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to Innovative High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

9:30 am: Welcome and Opening Remarks

9:45 am: Presentation of the Evidence

Evidence Review: Ethan Balk, MD, MPH, Brown University
Thomas Trikalinos, MD, PhD, Brown University

Cost Effectiveness: Karen Kuntz, ScD, University of Minnesota

11:00 am: Public Comments and Discussion

11:45 am: Lunch

12:45 pm: Midwest CEPAC Deliberation and Votes

2:15 pm: Policy Roundtable

3:30 pm: Reflections and Wrap Up

4:00 pm: Meeting Adjourned

Evidence Review

Thomas Trikalinos, MD, PhD

Ethan Balk, MD, MPH

Center for Evidence Synthesis in Health

Brown University School of Public Health

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Key Review Team Members

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Disclosures:

We have no conflicts of interest relevant to this report.

Cystic Fibrosis (CF)

- The most common life-shortening genetic disorder in white people
- Autosomal recessive trait (~1:3000 births, varies by race)
- Progressive disease that adversely affects respiratory function, nutrition, and growth

Pathogenesis

- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene
- CFTR protein regulates salt transport across cell membranes
- >1800 CFTR mutations associated with CF; ~300 fully characterized
- Result in absent, non-functioning, or abnormally functioning CFTR protein on cell membrane

Clinical Presentation, Respiratory

- Thickened secretions in organ lumens result in progressive organ damage
- Lungs
  - Infections early in life
  - Chronic and exacerbated infection damages bronchial wall and diminishes lung function
  - End stage disease results in lung failure and death

Clinical Presentation, Other

- Gastrointestinal system
  - Pancreatic insufficiency
  - Malnutrition; low weight /growth
- Endocrine system
  - Diabetes
- Reproductive system
  - Low fertility (women), infertility (men)

Management, Disease

- Early diagnosis and treatment may result in better nutritional and pulmonary outcomes later in life

- Symptom and complication control
  - Airway hygiene
  - Nutritional support, diet
  - Insulin
  - Treatment of exacerbations

- Disease modulation
  - CFTR modulators

Management, Other

- Comprehensive monitoring and treatment approach
- Burdensome for patients and caregivers
- Costly
- Adherence can be an issue

CFTR Modulator Drugs

- ↑ Cl^- transport through ion channel (gating)
  - **Ivacaftor**
- ↑ Transport of CFTR protein to cell membrane
  - **Lumacaftor**
  - **Tezacaftor**

- **Kalydeco® (ivacaftor)** FDA approved 2012
- **Orkambi® (lumacaftor/ivacaftor)** approved 2015
- **Symdeko™ (tezacaftor/ivacaftor)** approved 2018

Indications

- **Kalydeco** (ivacaftor)
  - "Gating" and residual function mutations
    - To increase ion transport across the cell membrane
- **Orkambi** (lumacaftor/ivacaftor)
  - *F508del* mutation, homozygous (2 copies)
    - To increase protein transfer to and ion transport across the cell membrane
- **Symdeko** (tezacaftor/ivacaftor)
  - *F508del* mutation, homozygous (2 copies)
  - *F508del* mutation, heterozygous (1 copy with a 2nd residual function mutation)
  - Other, rarer responsive mutations
    - To increase protein transfer to and ion transport across the cell membrane

Scope of the Review: PICO, 1

- **Population**: Adults and children with CF
  1. Gating and residual function mutations
  2. *F508del* homozygous
  3. *F508del* heterozygous with 2nd residual function mutation
- **Interventions**: Indicated CFTR modulators
  - With best/standard supportive care
- **Comparators**: No or other CFTR modulators
  - With best/standard supportive care

Scope of the Review: PICO, 2

Patient-centered clinical outcomes and harms

- **ppFEV$_1$** (% predicted forced expiratory volume 1 sec)
- **Pulmonary exacerbations**
- **Quality of life**
  - CFQ-R Respiratory Domain (CF questionnaire, revised)
- **Weight and growth**
- **Death, hospitalizations, lung transplantation**
- **Harms/adverse events**
- Fertility, pancreatitis, functional status, mental health, work/school, social function, finances, caregiver/family burden

Evidence Base

1. Kalydeco for gating and residual fxn mutations
- 4 RCTs in 3 specific populations (by mutation)
- 1 matched cohort in all indicated patients
- 1 pre-post cohort in all indicated patients (not in report)
  - All ≥ 6 years old

2a. Orkambi for homozygous *F508del*
- 3 RCTs (6-11 y/o and ≥12 y/o)

2b. Symdeko for homozygous *F508del*
- 1 RCT (mean age 26 y/o)

3. Symdeko for heterozygous *F508del*
- 1 cross-over RCT, with Kalydeco (≥12 y/o)

Kalydeco for Gating & Resid Fxn Mutations

Studies	$ppFEV_1$ (Abs Difference), % Points	Pulmonary Exacerbations	CFQ-R RD (Difference)
G551D Mutation (Randomized Controlled Trials)			
STRIVE ENVISION	10.4 (8.6, 12.3)	HR 0.46 (0.29, 0.73)	9.7 (6.5 to 13.0)
Non-G551D Mutation (Randomized Controlled Trial)			
KONNECTION	10.7 (7.3, 14.1)	nd	9.6 (4.5, 14.7)
R117H Mutation (Randomized Controlled Trial)			
KONDUCT		HR 0.93 (nd)	
6-11 y/o (N=17)	−6.3 (−12.0, −0.7)		−6.1 (−15.7, 3.4)
≥18 y/o (N=50)	5.0 (1.2, 8.8)		12.6 (5.0, 20.3)
Any Indicated Mutation, Implied (Matched Cohort Study)			
US Cohort		RR 0.64 (0.58, 0.70)	

Abs: absolute, **HR:** hazard ratio, **nd:** no data (not reported), **$ppFEV_1$:** predicted forced expiratory volume in 1 second, **CFQ-R RD:** Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure), **RR:** risk ratio, **y/o**: years old.

Kalydeco for Gating and Residual Function Mutations, Other Outcomes

- US Cohort N=1256 vs. 6000 matched controls
  - Any indicated mutation (implied)
  - 1 year follow-up
    - Death: RR **0.41 (0.20, 0.84)**
    - Organ Transplant: RR **0.15 (0.04, 0.59)**
    - Hospitalization: RR **0.64 (0.58, 0.70)**

- US Cohort pre-post Rx N=143 (not in report)
  - Any indicated mutation
  - 1 year periods
    - Hospitalization, all: 55% reduction (MC 38%)
    - Hospitalization, CF: 81% reduction (MC 46%)
      - And associated lower costs
      - Smaller reductions in Medicaid sample (N=100)

Orkambi & Symdeko for Homozygous *F508del*

Studies	$ppFEV_1$ (Abs Difference), % Points	Pulmonary Exacerbations (Rate Ratio)	CFQ-R RD (Difference)
Orkambi vs. Placebo			
Ratjen et al.	**2.4 (0.4, 4.4)**	nd	2.5 (−0.4, 5.4)
TRAFFIC TRANSPORT	**2.8 (1.8, 3.8) 42% slower rate of decline**	**0.61 (0.49, 0.76)**	**2.2 (0.0, 4.5)**
Symdeko vs. Placebo			
EVOLVE	**4.0 (3.1, 4.8)**	**0.53 (0.34, 0.82)**	**5.1 (3.2, 7.0)**
Symdeko vs. Orkambi			
Evolve vs. Tr/Tr (Network Meta-analysis)	1.2 (−0.1, 2.5)	0.87 (0.53, 1.42)	2.9 (0.0, 5.8)

Abs: absolute, **nd**: no data (not reported), **$ppFEV_1$**: predicted forced expiratory volume in 1 second, **CFQ-R RD**: Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure), **Tr/Tr**: TRAFFIC and TRANSPORT (combined).

Symdeko for Heterozygous *F508del*

Study	$ppFEV_1$ (Absolute Diff), % Points	Pulmonary Exacerbation, Rate Ratio	CFQ-R Respiratory Domain (Difference)
EXPAND	**6.8 (5.7, 7.8)**	0.54 (0.26, 1.13)	**11.1 (8.7, 13.6)**

Diff: difference, **$ppFEV_1$:** predicted forced expiratory volume in 1 second, **CFQ-R RD:** Cystic Fibrosis Questionnaire-Revised Respiratory Domain (quality of life measure).

Harms with CFTR Modulators

- Adverse events generally mild or self-limited
  - No reported deaths ascribed to drugs
- Adverse events common with placebo
  - Often higher than with drugs

- Orkambi
  - Chest tightness: ~10-20%
  - Drug discontinuation due to adverse event: 6%

Controversies and Uncertainties

- Unknown comparative value for several clinical outcomes of interest, particularly non-pulmonary effects

- Long-term effects on health, quality of life, treatment burden, management costs unknown

- Standard of care variable, even in studies and may impact incremental benefit
  - May be a particular issue in US, which lags other comparable countries in health status and survival

Evidence Ratings

- Kalydeco for gating mutation (*G551D, R117H,* other)
  - "**A**" (**superior**, high certainty substantial benefit)
- Orkambi for homozygous *F508del*
  - "**B**" (**incremental**, high certainty of small benefit)
- Symdeko for homozygous *F508del*
  - "**B+**" (**incremental or better**, moderate certainty of small or substantial benefit, high certainty of at least a small benefit)
- Symdeko for heterozygous *F508del*
  - "**B+**" (**incremental or better**, moderate certainty of small or substantial benefit, high certainty of at least a small benefit)

Other Potential Benefits and Contextual Considerations

- If effective, **may reduce burden** of therapy, caregiver/family burden, school/work, social stressors and functional status
  - No evidence for this
  - Caregivers concerned that increased pill burden
- **Health disparities** may be exacerbated among commercially insured
- **Novel treatments**. First to directly target dysfunctional proteins.

Public Comments Received

- Review does not adequately account for disease severity and the multi-system nature of CF
  - Nutrition versus respiratory
  - Other outcomes not in literature (e.g., diabetes)

- Not adequately capturing benefits and risks
  - Orkambi has more side effects than Symdeko
  - ppFEV1 and pulmonary exacerbation definitions
  - Minimally clinical important differences (MCID)

Summary

- Among those ≥6 years old, CFTR modulators generally
  - Improve ppFEV1
  - Reduce rates of pulmonary exacerbations
  - May improve respiratory-related quality of life.
  - May reduce death, transplantation, hospitalizations
    - Most evidence 6-12 months follow-up
    - Some evidence of maintenance of effects for up to 3 years

- Harms appear to be non-serious and self-limited
  - Orkambi has risk of chest tightness, likely resulting in higher rate of discontinuation for adverse events

Cost-Effectiveness

Karen Kuntz, ScD

Kael Wherry, MS

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Disclosures:

- We have no conflicts of interest relevant to this report.

Objective

To compare lifetime health effects, costs, and cost-effectiveness of CFTR modulator treatment plus best supportive care versus best supportive care alone for cystic fibrosis patients

Methods in Brief

Methods Overview

- **Comparators**: CFTR drugs + best supportive care (BSC), BSC alone
- **Populations**: Described on next slide
- **Model**: Discrete-time microsimulation model
- **Setting**: United States
- **Perspective**: Payer
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: Annual

- **Primary Outcomes:**
  - Lifetime cost (2017 US dollars)
  - Quality-adjusted life years (QALYs) gained
  - Life years gained
  - Acute pulmonary exacerbations
  - Incremental cost-effectiveness ratios

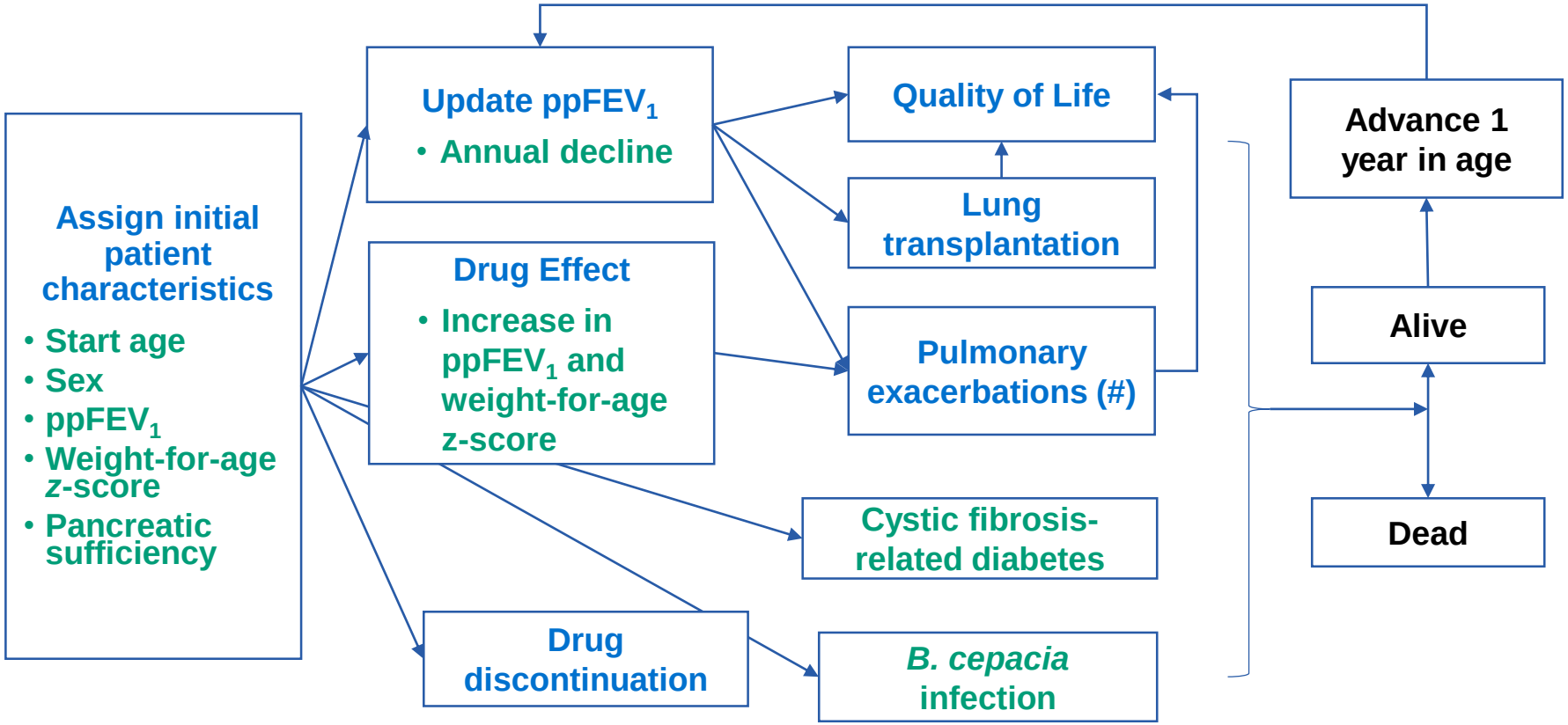
Populations and CFTR Modulators

1. **CF individuals with gating mutation**
   - Kalydeco (ivacaftor) at age 2

2. **CF individuals homozygous for *F508del* mutation**
   - Orkambi (lumacaftor/ivacaftor) at age 6
   - Symdeko (tezacaftor/ivacaftor) at age 6

3. **CF individuals heterozygous for *F508del* mutation with residual function mutation**
   - Symdeko (tezacaftor/ivacaftor) at age 12
   - Kalydeco (ivacaftor) at age 12

Model Schematic



CFTR Modulator Effectiveness

- Impact on $ppFEV_1$
  - Immediate increase in $ppFEV_1$
  - No change for first two years
  - Annual declines in $ppFEV_1$, 50% of that without drug
- Impact on weight-for-age *z*-score
  - Immediate increase in *z*-score; constant for lifetime
- Independent effect on pulmonary exacerbations
  - Changes in $ppFEV_1$ reduce PEx
  - We modeled an independent reduction and calibrated to the RR reported in trials

Direct Costs by Disease Severity

	$ppFEV_1 \geq 70\%$	$ppFEV_1$ 40%-69%	$ppFEV_1 < 40\%$
Disease Management	$25,367	$33,462	$57,210
PEx* (age <18)	$52,988	$83,956	$124,386
PEx* (age 18+)	$48,015	$76,322	$109,372
Lung Transplant	$905,191		
Post-Transplant (Year 1)	$273,665		
Post-Transplant (Year 2+)	$103,913		

* PEx = pulmonary exacerbation requiring IV antibiotics

Economic Inputs: Annual Drug Costs

CFTR Modulator Drug	Annual Drug Cost
Kalydeco	$309,842
Orkambi	$264,086
Symdeko	$282,656

WAC from REDBOOK; net price from Federal Supply Schedule

Modified Societal Perspective

- Loss of productivity
  - Inability to work (lower unemployment rates)
  - Due to illness (associated with pulmonary exacerbation)
- Caregiver burden
  - No direct evidence on reduction in caregiver burden with CFTRm drugs
  - Evidence that there is no relationship between caregiver burden and ppFEV$_1$

Clinical Inputs: Quality of Life Values

	EQ-5D Utility	Comparable to:
$ppFEV_1$	(Schechter 2015)	
>90	0.920	
80-89	0.873	
70-79	0.838	
60-69	0.801	
50-59	0.765	
40-49	0.729	
30-39	0.692	
20-29	0.653	
<20	0.625	
Acute Pulmonary Exacerbation	-0.174	
Lung Transplantation		
Year 1	0.320	
Year 2+	0.838	

Results

Lifetime Health Outcomes

Population and Treatment	Average Number of PEx	Total Life Years	Total QALYs
CF Individuals with a Gating Mutation			
BSC	32.75	22.16	15.92
Kalydeco + BSC	18.86	26.52	22.65
CF Individuals Homozygous for *F508del* Mutation			
BSC	26.02	20.77	14.74
Orkambi + BSC	11.45	24.57	20.21
Symdeko + BSC	13.36	24.70	20.25
CF Individuals Heterozygous for *F508del* with Residual Function Mutation			
BSC	25.51	18.98	12.92
Symdeko + BSC	12.68	23.25	18.88
Kalydeco + BSC	10.85	23.07	18.74

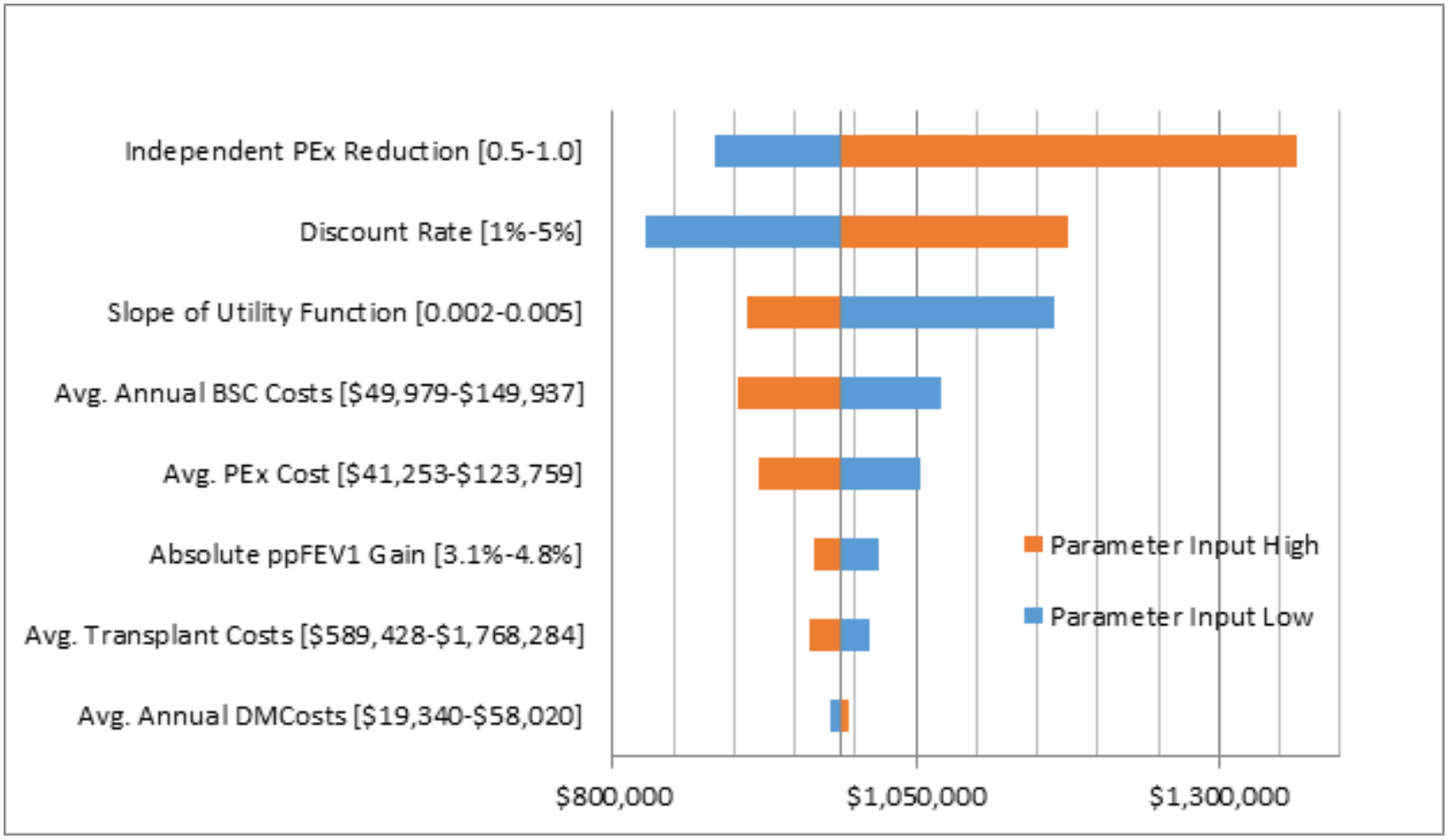
Lifetime Costs (2017 US dollars)

Population and Treatment	CFTR Modulator Drug Cost	Total Direct Cost
CF Individuals with a Gating Mutation		
BSC	$0	$2,227,765
Kalydeco + BSC	$7,443,121	$8,666,308
CF Individuals Homozygous for *F508del* Mutation		
BSC	$0	$2,108,199
Orkambi + BSC	$5,847,893	$6,983,336
Symdeko + BSC	$6,290,005	$7,478,684
CF Individuals Heterozygous for *F508del* with Residual Function Mutation		
BSC	$0	$2,081,180
Symdeko + BSC	$5,934,935	$7,091,919
Kalydeco + BSC	$6,447,156	$7,557,596

Overall Incremental Results

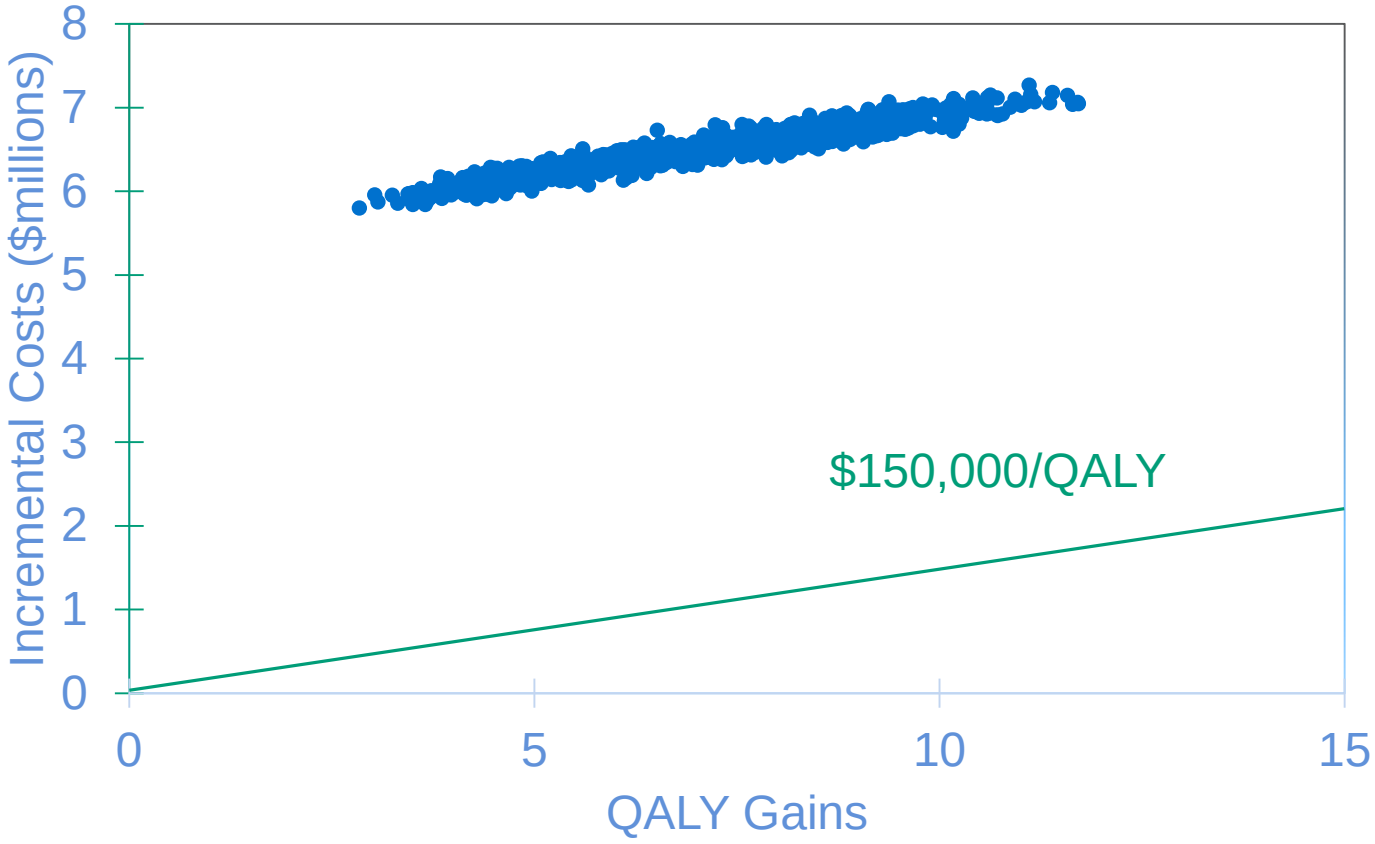
Treatment vs. BSC	Cost Per LY Gained	Cost Per QALY Gained	Cost Per PEx Averted
CF Individuals with a Gating Mutation			
Kalydeco + BSC	$1,476,543	$956,762	$463,571
CF Individuals Homozygous for *F508del* Mutation			
Orkambi + BSC	$1,280,892	$890,739	$334,495
Symdeko + BSC	$1,367,400	$974,348	$424,212
CF Individuals Heterozygous for *F508del* and Residual Function Mutation			
Symdeko + BSC	$1,174,508	$840,568	$390,600
Kalydeco + BSC	$1,340,171	$941,110	$373,541

Sensitivity Analyses (Symdeko, homozygous)



PEx: acute pulmonary exacerbation; BSC: best supportive care; DM: disease management; Probability of transplant among individuals with $ppFEV_1$<30%

Probabilistic Sensitivity Analysis (PSA)
(Kalydeco for gating mutations)



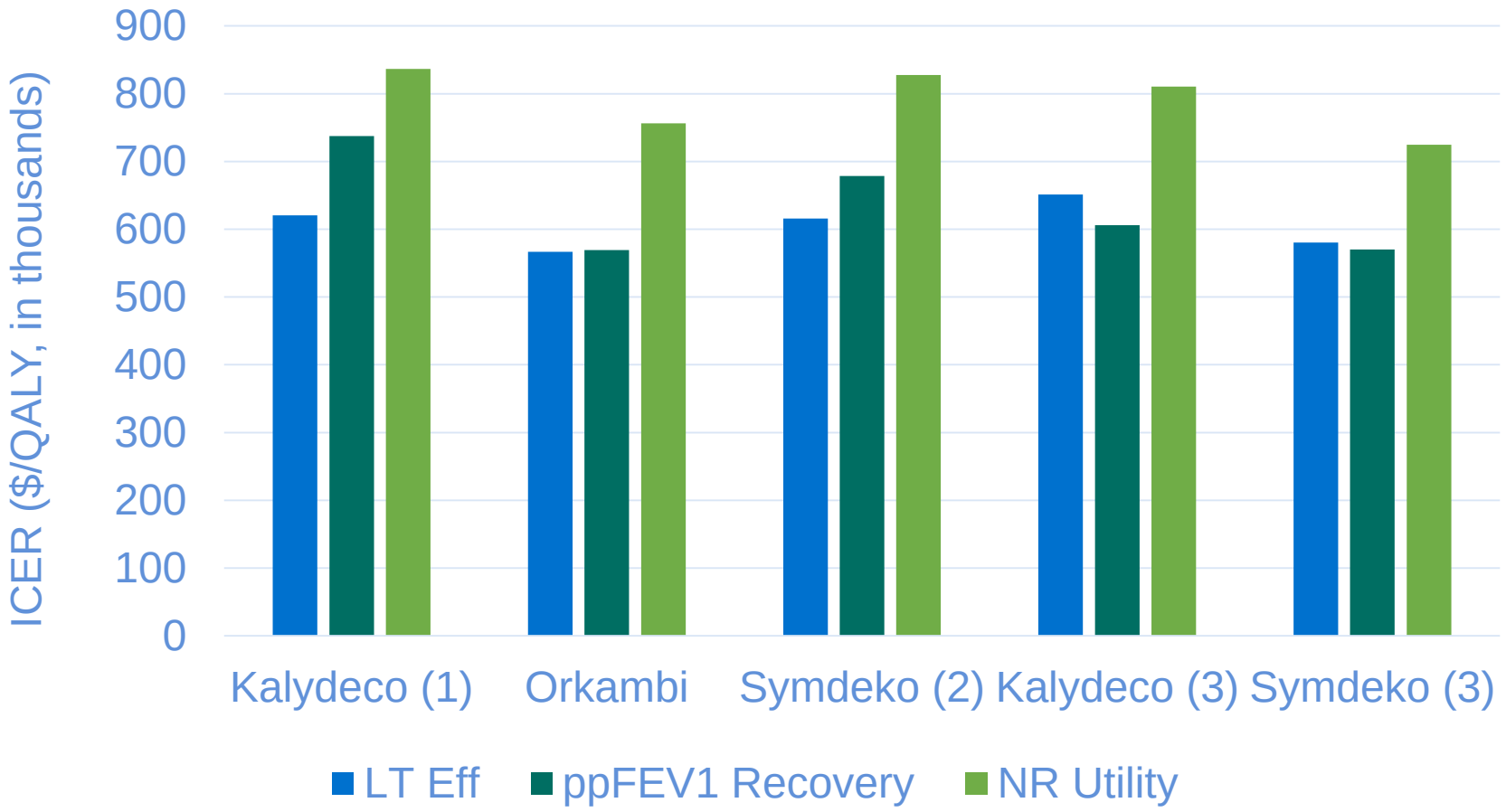
Scenario Analyses – Modified Societal Perspective

Treatment vs. BSC	Incremental Costs (Direct)	Incremental Costs (Indirect)	Cost Per QALY Gained
CF Individuals with a Gating Mutation			
Kalydeco + BSC	$6,438,543	-$31,635	$952,061
CF Individuals Homozygous for *F508del* Mutation			
Orkambi + BSC	$4,875,137	-$30,639	$885,140
Symdeko + BSC	$5,370,485	-$30,891	$968,744
CF Individuals Heterozygous for *F508del* and Residual Function Mutation			
Symdeko + BSC	$5,010,739	-$27,306	$835,987
Kalydeco + BSC	$5,476,416	-$26,054	$936,633

Scenario Analyses

- Long-Term Effectiveness Assumption
  - Best case: No long-term decline in $ppFEV_1$ with CFTR modulator drug
- $ppFEV_1$ Recovery After Pulmonary Exacerbation
  - Best case: There is a 5% absolute decline in $ppFEV_1$ for each pulmonary exacerbation experienced
- Independent Utility Effect
  - Best case: CFTR modulator drugs result in a 5% increase in utility, above that due to lung function improvements

Scenario Analyses Results (Best Case)



Limitations

- Modeled lifetime outcomes derived from short-term trial outcomes
- As with any surrogate marker of disease, ppFEV$_1$ is not a perfect marker for progression
- We did not have a direct measure of CFTR modulator benefit on utilities

Public Comments Received

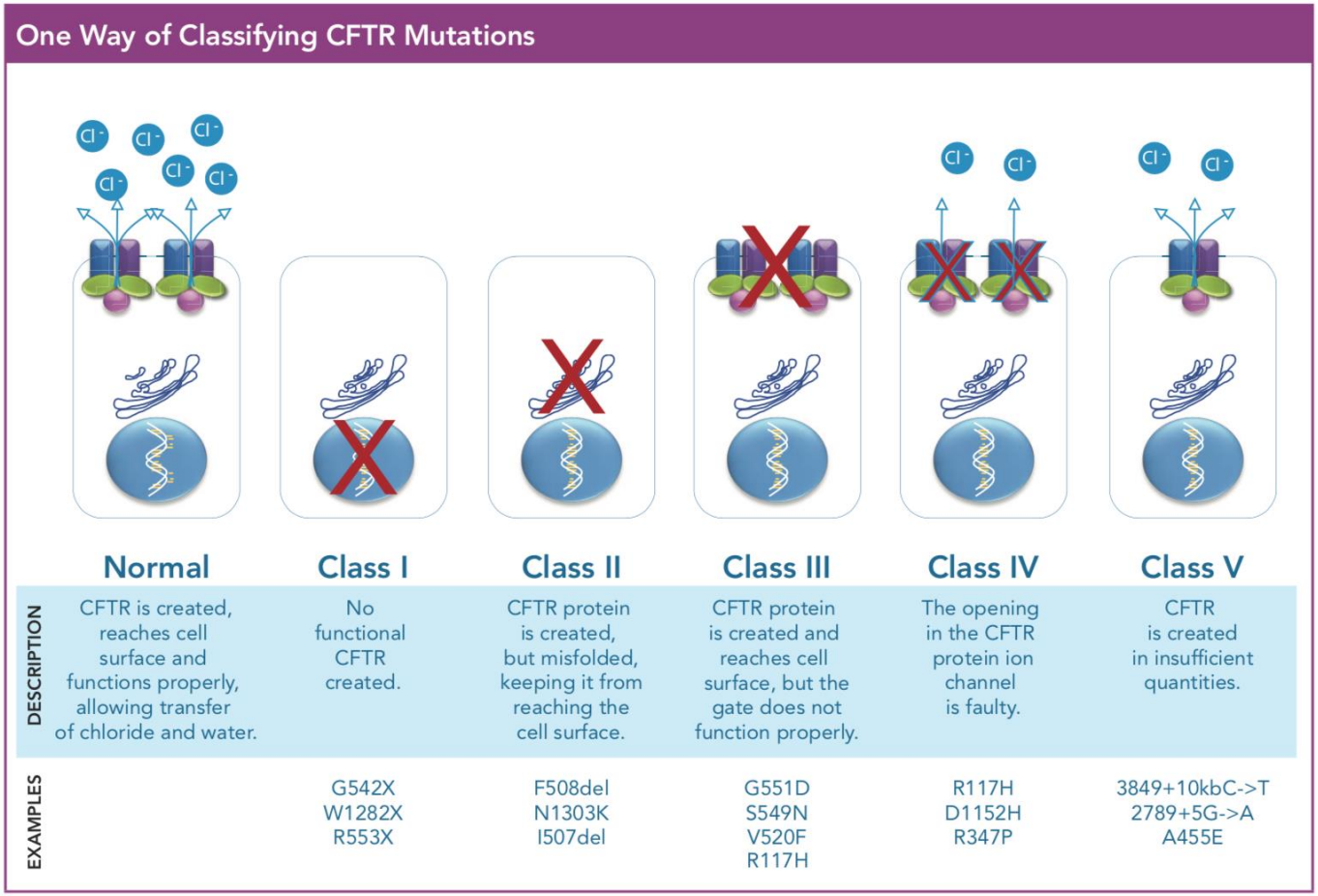
- QALY collapses multifactorial benefits of CFTR modulator into single outcome measure that does not capture overall impact to multiple organ systems
- Did not include societal perspective in base case
- Did not include potential changes in cost of CFTRm over time

Summary

- CFTR modulator therapies plus best supportive care improves health outcomes compared with best supportive care alone.
- However, in proportion to the clinical benefits, the added costs of CFTR modulator therapies exceeds commonly used thresholds for cost-effectiveness.
- The modified societal perspective scenario analysis did not notably improve the cost-effectiveness of CFTR modulator therapies.

Backup Slides

A classification of CFTR mutations



Key Model Assumptions and Inputs

- ppFEV$_1$ does not increase over time
- Best supportive care is the same in all treatment arms (conditional on ppFEV$_1$ category; as ppFEV$_1$ worsens, supportive care costs increase)
- Treatment discontinuation rates are same as reported in trials, with no further discontinuation after end of trials' time horizon

Clinical Inputs: Drug Effectiveness*

Treatment	Increase in ppFEV1	Change in weight-for-age z-score	Pulmonary exacerbation RR
CF Patients with Gating Mutation			
Kalydeco	10.0 (4.5-15.5)	0.35 (0.20-0.51)	0.56
CF Patients Homozygous for *F508del* Mutation			
Orkambi	2.8 (1.8-3.8)	Same as above	0.44
Symdeko	4.0 (3.1-4.8)	Same as above	0.54
CF Patients Heterozygous for *F508del* with Residual Mutation			
Symdeko	6.8 (5.7-7.8)	Same as above	0.54
Kalydeco	4.7 (3.7-5.8)	Same as above	0.46

*evidence report

Threshold Price Analysis

			Annual Price to Achieve				
	Annual WAC	Annual Net Price	$50K/ QALY	$100K/ QALY	$150K/ QALY	$500K/ QALY	
CF Individuals with a Gating Mutation							
Kalydeco	$311,719	$309,842	$55,145	$69,142	$83,146	$181,149	42%
CF Individuals Homozygous for *F508del* Mutation							
Orkambi	$272,886	$264,090	$55,562	$67,820	$80,063	$165,824	39%
Symdeko	$292,258	$282,850	$53,210	$65,467	$77,718	$163,501	43%
CF Individuals Heterozygous for *F508del* and Residual Function Mutation							
Kalydeco	$311,719	$309,842	$60,295	$74,175	$88,054	$185,211	41%
Symdeko	$292,258	$282,850	$57,921	$71,969	$86,016	$184,356	37%

Discount to achieve $500,000/QALY

Manufacturer Public Comment and Discussion

Vertex Pharmaceuticals

Public Comment and Discussion

Michael Boyle, MD
Senior Vice President of Therapeutics Development
Cystic Fibrosis Foundation

Conflicts of interest:

- Employee of Cystic Fibrosis Foundation (CFF), which provides research and clinical trial support to health care companies, including Vertex Pharmaceuticals, that results in the Foundation's receipt of payments, equity interests, and/or fees for service >$5,000 from Vertex Pharmaceuticals and other healthcare companies.
- Dr. Boyle is also an uncompensated Adjunct Professor of Medicine at Johns Hopkins University.

Siri Vaeth, MSW
Associate Director
Cystic Fibrosis Research Inc.

Conflicts of interest:

- CFRI provides a broad range of educational, psychosocial, and advocacy programs that receive grant funding from several pharmaceutical companies, including Vertex.
  - These grants are in support of specific CFRI programmatic goals and objectives to serve the nationwide cystic fibrosis community and have no relationship to specific drug therapies.

Chad Riedy
Person with Cystic Fibrosis
National Advocacy Co-Chair, Cystic Fibrosis Foundation

Conflicts of interest:

- National Advocacy Co-Chair at CFF, volunteer position.
- CFF paid for travel expenses to this meeting.

Mike Price
Parent of a Child with Cystic Fibrosis

Conflicts of interest:

- No relevant conflicts of interest to report

Juliana Keeping
Parent of a Child with Cystic Fibrosis
Communications Director, Patients for Affordable Drugs

Conflicts of interest:

- Owns shares of stock in Vertex Pharmaceuticals
- Patients for Affordable Drugs is funded in part by the Laura and John Arnold Foundation, which also provides funding to ICER.

Lunch

Meeting will resume at 12:30 pm

Voting Questions

WIFI network: TritonNet
Login ID: gst-cianciolola
Password: +3$nTaK=

What is Missouri's official state insect?

A. 7-spotted ladybug
B. European honey bee
C. Tarantula hawk wasp
D. Monarch butterfly

1. For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), is the evidence adequate to demonstrate that the net health benefit of treatment with Kalydeco (ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes

B. No

2. For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Orkambi (lumacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes

B. No

3. For individuals who are homozygous for the F508del mutation, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko (tezacaftor/ivacaftor) with best supportive care is greater than that of best supportive care alone?

A. Yes

B. No

4. For individuals who are homozygous for the F508del mutation, is the evidence adequate to distinguish the net health benefit between treatment with Symdeko with best supportive care and Orkambi with best supportive care?

A. Yes

B. No

5. For individuals who are candidates for Symdeko combination therapy because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, is the evidence adequate to demonstrate that the net health benefit of treatment with Symdeko with best supportive care is greater than that of best supportive care alone?

A. Yes

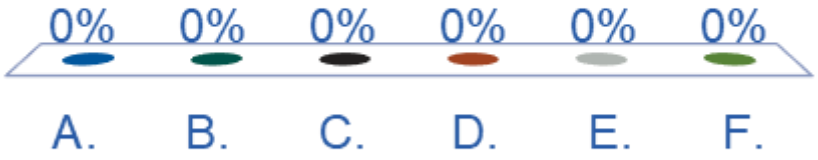
B. No

When compared to best supportive care, does Kalydeco, Orkambi, or Symdeko offer one or more of the following "other benefits"? (select all that apply)

A. Reduced complexity that will significantly improve patient outcomes.
B. Reduce important health disparities
C. Significantly reduce caregiver/family burden
D. Novel mechanism of action or approach…
E. Significant impact on improving return to work/overall productivity
F. Significant positive impact outside the family, including on schools and/or communities.
G. Significant impact on the entire "infrastructure" of care...
H. Other…

Are any of the following contextual considerations important in assessing Kalydeco, Orkambi, or Symdeko's long-term value for money in patients? (select all that apply)

A. Care of individuals with a condition of particularly high severity
B. Care of individuals with condition with high lifetime burden of illness.
C. First to offer any improvement
D. Compared to best supportive care, there is significant uncertainty about the long-term risk of serious side effects
E. Compared to best supportive care, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
F. Additional considerations…

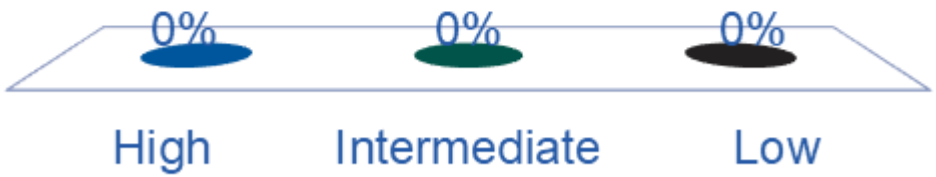


6. For individuals with approved gating, non-gating, and residual function mutations (including but not limited to G551D and R117H), given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Kalydeco with best supportive care compared with best supportive care alone?

A. High

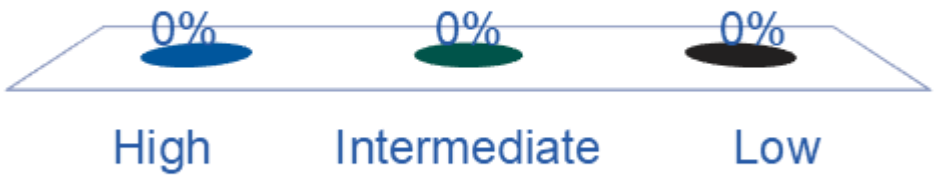
B. Intermediate

C. Low



7. For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Orkambi with best supportive care compared with best supportive care alone?

A. High
B. Intermediate
C. Low

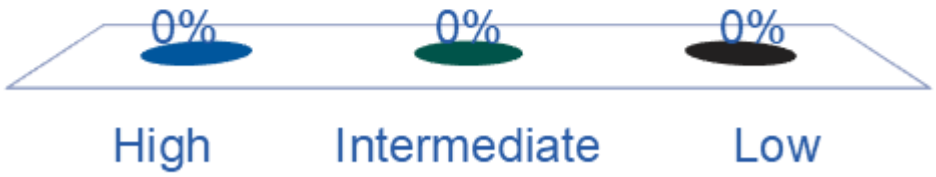


8. For individuals who are homozygous for the F508del mutation, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with best supportive care alone?

A. High

B. Intermediate

C. Low

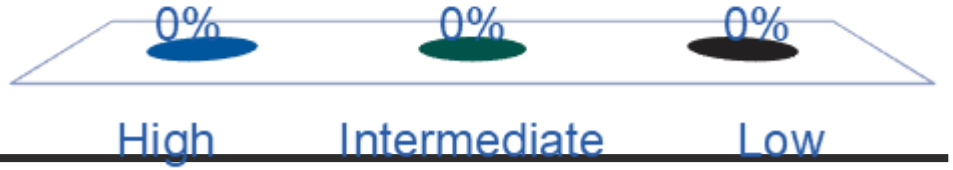


9. For individuals who are candidates for Symdeko because they carry one F508del mutation and residual function mutation that is potentially responsive to Symdeko, given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of Symdeko with best supportive care compared with supportive care alone?

A. High

B. Intermediate

C. Low



Policy Roundtable

Policy Roundtable Participants

Name	Title	COI Declaration
Mary Dwight	Senior Vice President of Policy and Advocacy Cystic Fibrosis Foundation	CFF provides research and clinical trial support to health care companies, including Vertex Pharmaceuticals. CFF has received charitable contributions and/or fees for service >$5,000 from Vertex Pharmaceuticals and other health care companies.
Jane Horvath, MHSA	Senior Policy Fellow National Academy for State Health Policy	Employee of the National Academy for State Health Policy.
Manu Jain, MD, MS	Professor of Medicine and Pediatrics, and Director of Adult CF Feinberg School of Medicine, Northwestern University	Member of the Vertex Pharmaceuticals Advisory Board, and Site PI for Vertex Phase 2 and 3 studies. Has received more than $5,000 in honoraria or consultancies during the previous year.
Jeremy Olimb	Pastor and father of children with cystic fibrosis	No conflicts of interest to report.
David Orenstein, MD, MA	Antonio J and Janet Palumbo Professor of Cystic Fibrosis Children's Hospital of Pittsburgh	No conflicts of interest to report.
Erik Schindler, PharmD, BCPS	Manager, Clinical Pharmacy UnitedHealthcare Pharmacy	Employee of UnitedHealthCare.

Midwest CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about June 7
  - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Materials available at:

  https://icer-review.org/topic/cystic-fibrosis/

Adjourn