



Cystic Fibrosis

Response to Public Comments on Draft Evidence Report

May 3, 2018

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#	Comment	Response/Integration
Manufacturers		
Vertex Pharmaceuticals		
1.	<p>As we have noted in previous letters, we continue to believe that ICER’s framework does not appropriately capture the overall impact of innovative, life-extending therapies for rare diseases, such as CFTRm. Kalydeco, Orkambi, and Symdeko have all been granted orphan and breakthrough drug designations from the Food and Drug Administration (FDA), and have been shown to have significant clinical benefits for the patients who are eligible for Vertex’s currently marketed cystic fibrosis (CF) therapies. Kalydeco and Orkambi have shown improvements across a range of important clinical outcomes, including short-term increases in lung function as well as long-term reductions in the rate of lung function decline. While Symdeko has not yet been studied for long-term rate of decline due to its recent approval in February 2018, patients treated with Symdeko experienced statistically significant and clinically meaningful improvements in lung function and other measures of disease, with a favorable safety profile. CFTRm offer major improvements in quality of life and/or length of life for many patients with CF and we remain concerned that ICER’s framework does not adequately capture the full benefit of these therapies to patients, their families and society at large.</p>	<p>Thank you for your comment. It is not clear to us why there is concern about our framework’s ability to capture the benefits of the CFTR modulators, as our model was built on improvements in lung function, reductions in long-term functional decline, and independent effects on pulmonary exacerbations. In addition, we conducted a scenario analysis using a modified societal perspective to capture effects outside the health care system, and highlighted several contextual considerations as well as other benefits enumerated by the framework but outside of our explicit modeling exercise.</p>
2.	<p>In addition, we are concerned that the analysis is not constructive from a patient access perspective. Currently, there is widespread access—from both public and private payers—to Kalydeco and Orkambi for eligible patients in the United States, thereby demonstrating the value payers see in these medicines and further calling into question the utility of ICER’s review. We are concerned that the public release of a flawed analysis may diminish access to these therapies. We believe ICER’s framework to be ill-suited for complex, rare diseases such as CF and are concerned that the consequence may be increased restrictions to “the only available intervention that targets the basic pathophysiology of the disease” and the discouragement of innovative science.</p>	<p>The adaptation made to our framework for ultra-rare disease was informed by input and commentary from multiple stakeholders, including manufacturers of treatments for rare diseases. Rather than discouraging innovation, we feel that our mission is to produce rigorous examinations of the evidence that will lead to sustainable access to high value care for all patients. When prices are not aligned with value, this access is called into question.</p>
3.	<p>The Quality Adjusted Life-year collapses the multifactorial benefits of CFTRm into a single outcome measure that does not capture the impact to multiple organ systems of these treatments. In the ICER model, utility scores were assigned based on ppFEV1 and pulmonary exacerbations only, and thus all quality-of-life benefits of CFTRm are assumed to be mediated through respiratory improvements. This approach ignores documented benefits of CFTRm on other organ systems and general improvements in well-being and quality of life not related to respiratory outcomes. Importantly, the one-way sensitivity analysis in the report demonstrates that the model is most sensitive to assumptions regarding QoL (utility) versus all other parameters examined.</p>	<p>Robust utility data are available for lung function but not for other domains. More importantly, only one trial (for one drug) collected information on the non-respiratory domains of the CFQ-R, which indicates that there may be improvements in other domains that do not translate directly to an improvement in utility. To examine this potential effect, we now provide a scenario analysis where we allow an independent increase in an individual’s utility, but note that this change alone does not materially affect our primary findings.</p>

4.	<p>ICER did not include the societal perspective in the base-case because “[w]hile the impact of this disease on patient and caregiver productivity, informal caregiver time, education, and disability costs can be substantial, the impact of treatment with the CFTR modulators on societal costs is not expected to be as substantial, because the drugs do not greatly reduce the daily burdens associated with usual CF supportive care.” However, there are societal costs of the disease that CFTRm may improve in the short term, including loss of school and work time related to pulmonary exacerbations . Moreover, because CFTRm are expected to fundamentally alter the course of disease, their full societal impact on disability, educational attainment, and career trajectory for patients and family members, and the impact of freeing resources for more productive uses may not be known for decades, but are likely to be substantial. Because, in the model, all of the quality of life benefits are mediated through ppFEV1, ICER asserts that many aspects of the societal perspective, including caregiver costs, not intrinsically tied to ppFEV1 could not be captured. This highlights the limitations of this model in capturing the full benefits of these innovative medicines.</p>	<p>We found no direct data on how CFTRm affect productivity and educational attainment. Therefore, we used data on the relationship between productivity and lung function to infer what those benefits might be. We acknowledge this as a limitation and note the importance of collecting data on these important outcomes in future studies.</p>
5.	<p>The results of the one-way sensitivity analyses demonstrate that the ICER model is extremely sensitive to the chosen discount rate, which is second only to utility in driving the cost per QALY gained. Because CFTRm are required over the patients’ lifetimes and the benefits of CFTRm in the model are driven primarily by survival improvements that occur far into the future, benefits of therapy are heavily discounted and the denominator in the cost per QALY calculation is disproportionately impacted by the assumed discount rate. This high degree of sensitivity to the chosen discount rate in evaluations of lifelong therapies has been recognized by Health Technology Assessment agencies, most notably by NICE in England, who recommends that alternative discount rates (3.5 percent for costs and 1.5 percent for outcomes) should be considered for therapies where “treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years).” The disproportionate influence of the chosen discount rate in the ICER model highlights an inherent bias against lifelong therapies for chronic conditions with benefits accruing far into the future.</p>	<p>The most sensitive parameter estimate was in fact the assumption around independent effects on pulmonary exacerbations. While the discount rate was also a sensitive parameter, we note that cost-effectiveness ratios remained above \$700,000 per QALY gained even when using a discount rate of 1% for both costs and outcomes.</p>
6.	<p>ICER did not include changes in cost of CFTRm over time in their model, in contrast to the three published cost-effectiveness models on CFTRm that considered such pricing dynamics in their evaluations of these medicines. Instead, the ICER model assumes patients begin treatment at the earliest indicated age (6 years old in the case of lumacaftor/ivacaftor) and generally remain on treatment until death at a median age of 47 years (using the F508del homozygous treatments as an example). Over these ~40 years of treatment, the model assumes no reduction in the cost of CFTRm due to loss of exclusivity (LOE). This assumption unnecessarily biases the analysis against life-</p>	<p>ICER does not as a rule consider such “dynamic pricing” approaches in its modeling unless there is known timing for patent expiry and certainty around expected changes in price. This is rarely accomplished in practice because there is a high degree of variability in patent extension practices, delays in generic development, and other such factors. In addition, there is evidence that generic entry in the setting of rare diseases and limited competition does NOT</p>

<p>saving therapy used in chronically ill patients requiring life-long treatment. Assuming that the branded cost is retained over decades does not reflect real-world evidence of price reductions after LOE: IMS prescription data show that oral small-molecule drugs like CFTRm have an average price drop of 80 percent within five years of LOE, with these cost savings maintained over time. Inclusion of this LOE assumption is consistent with all published models examining CFTRm cost-effectiveness. Because the non-CFTRm treatments included in the ICER model's best supportive care (BSC) basket are generally generic, there would be little added complexity to implementing a LOE assumption when estimating cost of CFTRm treatment in the model. The failure to consider price reductions due to generic entry overstates the cost of innovative therapy and is another example of several arbitrary choices made in the model that are not supported by empirical evidence but substantially change the incremental cost-effectiveness ratios, and thus the value-based prices, derived from this modeling.</p>	<p>in fact lower prices substantially. For example, the recent launch of a generic version of trientine hydrochloride, a small molecule used for Wilson's disease, represented a 14% discount from the list price of the branded product (https://www.nytimes.com/2018/02/23/health/valeant-drug-price-syprine.html). While the models cited did in fact make a LOE assumption, this appears to be based on data supplied by Vertex, is highlighted as a key limitation in all publications, and in fact resulted in cost-effectiveness ratios much higher than commonly-accepted thresholds. Finally, the LOE assumption was publicly questioned by the NICE review committee evaluating Vertex's Orkambi submission (NICE appraisal consultation document: lumacaftor/ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. Page 35. March 2016).</p>
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Clinical Societies

Patrick Flume, MD. Medical University of South Carolina Cystic Fibrosis Center

1.	<p>The background is improved. I suggest you remove the reference to <i>Strep pneumoniae</i> as the initial cause of infection (their Page 2, but pdf page 8 and will use this numbering system) – this is not a typical pathogen and you would not want to lose an informed reader so early in the document.</p>	<p>Thank you, we have removed the reference to a specific pathogen.</p>
2.	<p>Clinical Presentation (page 9): the respiratory issues are not the most remarkable. In the early part of life, growth and nutrition might take precedent. I would just delete the opening sentence.</p>	<p>We agree. The sentence was removed.</p>
3.	<p>Management (page 10): I suggest you change CPT to airways clearance or acknowledge there are devices that are used as well</p>	<p>We have added “airway clearance devices” to the list.</p>
4.	<p>CFTR modulator drugs (page 11): the sentence "For example, patients who are homozygous..." needs to be deleted; the sentence preceding is fine. The 3rd paragraph needs to be edited as the correctors are indicated only for F508del, so the opening line must contain it, and you should not use the term e.g. (example gratia) when it should be i.e. (id est, or that is)</p>	<p>We removed the “For example” and removed ivacaftor (alone) from the paragraph. Otherwise, the paragraph is correct. We have retained “e.g.” as the example it was meant to be.</p>
5.	<p>More on that page: the final paragraph makes statements about data being "short term" but we now have data for years (both ivacaftor and lum/iva) and you suggest survival data do not exist. However, there are data on usage in patients with advanced stage disease (at least for ivacaftor) and prolongation of time to transplant. I think this do represent survival data.</p>	<p>We considered a maximum of 3 year follow-up to be relatively short-term. We have stated this more explicitly. We did not find substantive survival data. Prolongation of time to transplant is of interest, but is not the same as “increased survival.”</p>
6.	<p>Outcomes (page 14): why is transplantation not included?</p>	<p>We provide examples of clinical outcomes, not a complete list. However, we agree this is of sufficient interest and have added lung</p>

		transplantation as an example clinical outcome.
7.	Insights gained (page 18): I think you have this section right	Thank you for your comment.
8.	Potential cost savings (page 19): I am not sure what you are asking for in the statement "we are looking for information on low value services used in the management of CF beyond the potential offsets that arise from a new treatment". If we assume that all advice contained within CF guidelines have value (visits, screening, monitoring, treatments) what else is there? No doubt there are some medications used for which there are few data, or even recommendations against, but I am skeptical of the actual usage. Studies of stopping therapies (independent of CFTR modulators) such as macrolides, have not been done.	Thank you for your comment. Our intent is to have stakeholders highlight services provided to CF patients that are of questionable or low value as a means to generate budget headroom to pay for innovative new treatments. It may be the case that all current services are of high value, but this may vary by location and setting. We note in our revised report whether we received any feedback on this request.
9.	Coverage policies (page 20): Many insurance companies require submission of LFTs and some have inserted some language regarding adherence (e.g. refills) for continued use of the drugs	Thank you for the comment, this adds additional perspective on the variety of coverage policies. The coverage policies section of our report is not intended to be an exhaustive list, but rather a brief overview of some of the most common plans and coverage policies. We have not identified the language you mention in these policies, but will look to integrate these concerns in our final report if we receive appropriate citations.
10.	Respiratory Care Guidelines (page 21): inhaled antibiotics and dornase are recommended even in patients with mild disease (and normal lung function). Note that for the rating system used an A does not mean it has a greater recommendation than if given a B, just that the level of evidence is greater.	We have changed the wording to indicate that inhaled antibiotics and dornase alfa are recommended for all patients.
11.	Pulmonary exacerbations (page 22): The guidelines do not recommend against home IV; it is specifically stated that there is insufficient evidence upon which to make a recommendation.	Thank you for your comment. We have clarified the guideline statement in the revised report.
12.	NICE guidelines (page 23): This should be noted to be UK specific. There are also ECFS guidelines on antibiotics and standards of care	Thank you, we have added that NICE guidelines are written primarily for the UK. While we did not include a review of the ECFS guidelines, we note that they are very similar in scope and recommendations to those of the CFF and NICE. The Clinical Guidelines section is not intended to be an exhaustive review of all clinical guidelines, but rather a summary and sample of clinical guidelines.
13.	Ivacaftor data (page 35): Using exacerbations as a clinical endpoint requires a longer duration than was used for this study	We have added caveats to tables and text about the short duration of follow-up for this study.

14.	Exacerbations (page 36): I suggest not using the term "requiring IV antibiotics and hospitalization". This is what was done but I am not certain that it was required. I am not arguing that this is not relevant, but if we are to learn that we should be even more aggressive with management of exacerbations (e.g. all should get IV rather than oral, and hospitalization is much better than home therapy) how might that impact your results? Perhaps this might fit into the concept of "low value services"?	We modified the language to clarify that we are talking about the definitions of pulmonary exacerbation used (or reported) in studies, and discuss variability in level of detail reported as a limitation of available studies.
15.	Correctors (page 37): You should acknowledge the core differences between luma and teza, which include the drug-drug interactions and the adverse event of chest tightness/drop in FEV1. Teza also did not get the same results on BMI	We added a statement to the summary on clinical benefits that harms are discussed separately. The summary of BMI data is correct.
16.	More on correctors (page 40): You acknowledge a post-approval study (single site, 4 months) where luma/iva showed no difference, but this study had no comparator so this is not a legitimate assessment. Your methods allow for inclusion of single arm studies lasting >1 month. However, Table F purportedly offers assessment of trial ratings, but I don't see that information within the table and the methods note that this type of study would get no quality rating. So how relevant were these data in the inclusion of your meta-analysis? They should only be used for assessment of harms (again in the methods page 27), so then why does this study, which should not be used for clinical outcomes, get its own paragraph?	We do not give quality ratings for non-comparative studies, as many of the rating tools focus on domains that require a comparator (e.g., treatment group imbalances, differential attrition). These data were also not included in any meta-analysis of key endpoints. When assessing evidence, we prioritize comparative studies when such data exist. However, we do consider non-comparative studies to be part of the evidence base for both clinical benefits and harms, and when we feel that they add important context, we summarize them descriptively in the relevant sections.
17.	Controversies (page 54): The last paragraph addresses interpreting lung function changes. Although the FDA has not come out and stated what constitutes a meaningful magnitude of change as far as trial data are concerned, clinicians know that anything better than zero is a good day. More relevant however, is that the FDA approved luma/iva based on a 2-3% absolute change in lung function. While some may complain this is not much, dornase was approved based on a 5% relative change in lung function, and that generally equates to a 2-3% absolute change. So there is precedent for this value. The comment about change due to measurement variability is not relevant; these are population data, not individual data, and as you increase the number of subjects and data points, the variability becomes mere white noise, essentially canceled out (remember, the variability goes in both directions, up and down, with equal probability). The example of the Dutch study was regarding the individual, and is not relevant to this interpretation.	We have included that there is precedent for FDA approval based on 2-3% absolute change in ppFEV1, but maintain that this is not the same thing as an established minimum clinically-important difference, and still feel that the caveat still holds that data that this change translates to improved survival or quality of life are sparse. We've revised the report taking the measurement variability among individuals into consideration, and no longer cite this as a key uncertainty.
18.	Stakeholder comment (page 55): this one example (highlighted) is really problematic because this was most assuredly due to luma/iva where impact on lung function is known. This is not the case for tez/iva, nor iva alone	We have refined the commentary on the stakeholder comment to emphasize the difficulties in weighing tradeoffs and that not all patients will respond as expected based on study evidence.

19.	The very next paragraph left me perplexed; what does that opening sentence even mean? This paragraph should be deleted.	We have edited this paragraph for clarity. Through our review, we identified uncertainties discussed in a comparison of American and Canadian CF patient survival. This study observed differences in survival, favoring Canada by an average of 10 years, which may be accounted for by the disparities faced by those enrolled in public vs. private health insurance.
20.	Ratings (page 57): you have not included the data on rate of decline of lung function for luma/iva; I take issue on both the level of certainty and the size of health benefit. Rate of decline might play a much more relevant role as a clinical outcome. It serves poorly in clinical trials because of the number of subjects needed and the duration of the study, but now we have epidemiologic data to add certainty to the assessment.	We have more explicitly added in the rate of decline in FEV1 from the extension study (PROGRESS).
21.	Target population (page 61): we accept that all models are flawed. Not knowing how some of these points would influence the final outcome, it is still important to note that the proportion of patients on inhaled tobramycin and/or aztreonam is only applicable to those with <i>Pseudomonas</i> in cultures. One additional observation for CFTR modulators is the impact on microbiology with a lesser proportion growing <i>Pseudomonas</i> . Also, for those on inhaled antibiotics, the proportion on a continuous alternating treatment (CAT) regimen has been increasing meaning that many will be on both inhaled agents.	We included antibiotic use based on stakeholder comments to ensure complete costing of CF care for face validity purposes. We acknowledge that we are not micromodeling types of infections and that this is a limitation. This limitation has now been added to the report.
22.	Also, pulmonary exacerbations include more than just IV treated. We now know that these events are associated with drops in lung function that do not fully recover and that those treated in the outpatient setting, especially with oral drugs, seem to have worse outcomes.	We agree that pulmonary exacerbations include more than just those that are IV treated. However, the mortality model we and others have used (Liou) was based on pulmonary exacerbations that required IV antibiotics, and so we used that definition.
23.	Assumptions (page 62): the assumption that other costs of supportive care not associated with lung function will not be affected by a CFTR modulator is not entirely correct. There are reports of less sinus disease, reduced need for digestive enzymes, and reduction in CF related diabetes.	We found one reference that reported: "We did not find any change in the prevalence of exocrine pancreatic insufficiency or diabetes in patients treated with ivacaftor." (Hubert D 2017) This paper also showed a non-significant change in pancreatic enzymes. None of the other papers reported on these outcomes. We would need more evidence to model these effects, beyond individual case reports.
24.	Table of Key Model Inputs (page 64): there should be an attributed drop in lung function that is not recovered for each exacerbation. I could offer some thoughts on what that number should be, but it is likely about 5%.	While there is one paper we found that reports on this effect (Sanders DB 2010), it is difficult to determine what degree of the increase in ppFEV1 is due to this effect, or to what degree the reduction in the long-term decline in lung function is due to this effect. In addition, it is difficult to distinguish between the failure to recover from an

		<p>exacerbation and the expected decline in lung function over time.</p> <p>We added a scenario analysis to investigate the potential impact of this effect, where we varied the additional decline in ppFEV1 between 0 (no effect) and 5% (relative effect).</p>
25.	<p>Transplant-related costs (page 69): Suggest you justify why you are using 1995 costs? Although you have adjusted cost estimates to 2017 dollars, I am not sure it can be assumed that explains the entire difference. Also, I am suspicious of the dollars used for treatment of exacerbations. I have seen bill totals paid by Medicaid and insurance companies that exceed what has been reported.</p>	<p>We updated the lung transplantation costs using a 2017 reference (Milliman). We have also used other sources to update other estimates of the cost of best supportive care, which is now much greater than in our draft report.</p>
26.	<p>Base case results (page 71): did I miss how you have defined a QALY? I can see how you came up with dollars, and even dollars per QALY, but I reviewed the methods again and did not see how they derived the QALY.</p>	<p>QALYs represent survival multiplied by a quality-of-life weight (utility) associated with morbidity status. We added a description of QALYs in the methods section of the report.</p>
Patients / Patient groups		
Boomer Esiason, Boomer Esiason Foundation		
1.	<p>We understand that the intent of this review is to determine the cost-effectiveness of these medicines but why CF medicines and why now? We need these therapies not only because they are transformative for the thousands that are taking them each day, but, because they are the framework for what will be treatments for over 90 % of the CF population. We are concerned that this draft report may be used to create obstacles for patients to access those treatments today and stifle innovation for tomorrow.</p> <p>Thankfully, these past few decades of costly and tireless research have yielded major breakthroughs in the fight against CF and the underlying cause of the disease. These patients cannot be discriminated against due in large part to a mathematical formula. My math shows that we're halfway there. Please understand that while thousands of families are benefiting from these new discoveries, many continue to wait for drug options that will treat their son or daughter's specific type of CF. We are amongst those families: prescription drug treatments are still unavailable for Gunnar, and the other half.</p>	<p>Thank you for your comment. As we have stated above: rather than discouraging innovation, we feel that our mission is to produce rigorous examinations of the evidence that will lead to sustainable access to high value care for all patients. When prices are not aligned with value, this access is called into question.</p>
Preston W. Campbell III, MD, Cystic Fibrosis Foundation		
1.	<p>Potential benefits from long-term and early initiation of CFTR modulators</p> <p>As noted in the draft report, modulator therapies “substantially improve patient outcomes” when added to best supportive care. The development of cystic fibrosis transmembrane conductance</p>	<p>We feel that the potential for the CFTR modulators to alter the course of disease and improve quality of life are in fact reflected in our modeling approach, as the results indicate improvements of 35-40% in</p>

	<p>regulator (CFTR) modulators marked an important milestone in CF care. These treatments are the first to target the underlying defect in the CFTR protein caused by specific mutations of the <i>CFTR</i> gene. Short of a cure for CF, modulators have the potential to dramatically alter the course of this disease, particularly for those who start treatment at a young age. For such patients we anticipate a life span that approximates that of the general population with most, if not all, of the costs associated with current “standard of care” treatments potentially eliminated. An early start on modulators could have long-term benefits in sustaining health: 1) by reducing the rate of lung function decline through prevention of structural damage to the lungs and 2) improving nutrient absorption and weight gain through preservation of pancreatic exocrine function. While research on the impact of starting modulators early in life is underway, we urge ICER to fully acknowledge the potential benefit of early use of these therapies in examining their value over a lifetime in the report’s introduction, other benefits and contextual considerations section, and model assumptions.</p>	<p>quality-adjusted life expectancy in comparison to standard of care alone.</p>
<p>2.</p>	<p>Differences between lumacaftor/ivacaftor and tezacaftor/ivacaftor The draft evidence report notes that for individuals with two copies of the <i>F508del</i> mutation there is “no material difference in key clinical outcomes” for tezacaftor/ivacaftor versus lumacaftor/ivacaftor. However, real world experience with lumacaftor/ivacaftor and clinical trial results for tezacaftor/ivacaftor suggest important differences that can affect health outcomes. Of note, tezacaftor/ivacaftor is associated with fewer adverse events and drug-drug interactions compared to lumacaftor/ivacaftor. Tezacaftor/ivacaftor is a treatment option for those who could not take lumacaftor/ivacaftor due to chest tightness or drug contraindications such as oral contraceptives. The improvement in tolerability and reduction of drug-drug interactions represent a significant opportunity for individuals to benefit from modulators.</p>	<p>We were describing clinical benefits, distinct from adverse events. We have added a summary paragraph on clinical benefits stating that adverse events are described in a different section.</p>
<p>3.</p>	<p>Coverage policy landscape of CFTR modulators We appreciate ICER’s attention to coverage policies for CFTR modulators as the value of these drugs is only realized if patients can access them. The draft evidence report notes that modulator coverage typically involves prior authorizations that require documentation of specified starting age and <i>CFTR</i> mutations which reflect the label approved by the Food and Drug Administration (FDA). However, while the three plans ICER reviewed may provide coverage aligned with the FDA’s label there are a number of plans that have implemented more restrictive coverage criteria. In some cases, these criteria are clinically inappropriate, administratively burdensome, and create barriers to access. Some examples include:</p> <ul style="list-style-type: none"> • Use of clinical trial participation criteria to justify coverage exclusions: public and private payers cite lack 	<p>Thank you for the comment, this adds additional perspective to the variability in coverage policies. The coverage policies section of our report is not intended to be an exhaustive list, but rather a brief overview of some of the most common plans and coverage policies. That being said, if you can point us to examples of these criteria that we can cite, we will consider their inclusion for the final report.</p>

	<p>of evidence that drugs work for populations excluded from trials despite the FDA’s determination that the drug is safe and effective for anyone with an approved mutation;</p> <ul style="list-style-type: none"> • Increased frequency of reauthorization: payers asking repeatedly for patient’s mutation, which does not change over time; and • Requirements to be on other symptom-directed therapies as a condition of coverage without regard to the patient’s unique treatment regimen or medical needs. <p>It is also important to note that, as we look ahead, payers should take extreme caution when considering policies that prefer use of one modulator over another. Cystic fibrosis care is complex as providers consider a multitude of factors when prescribing treatment, therefore, clinician discretion and expertise should be upheld.</p>	
4.	<p>Model limitations</p> <p>We are pleased to see the initial economic model has been revised to include both ppFEV₁ and past pulmonary exacerbations as predictors of future pulmonary exacerbations. We recognize that not all available evidence is suited for this model. However, several of the remaining assumptions and data inputs, or lack thereof, impose significant limitations to the model. As we have stated previously, the costs derived from Lieu et al. and Ouyang et al. are not valid estimates for current standard of care. These papers are outdated and should not be generalized in the model. Further, while only utility scores by ppFEV₁ are available, we know that modulators have clinical and quality of life benefits beyond lung function. Finally, echoing our statement above, the model does not yet account for the anticipated long-term benefits of modulators. As experts in the pathophysiology of CF, we believe that early initiation and long-term use of modulators will have profound implications, altering the course of this disease by preventing structural damage to the lungs and preserving pancreatic exocrine function.</p>	<p>We obtained updated costs from MarketScan and Medicaid data (personal communication, Scott Grosse). We continue to use the Lieu paper to inform the relative costs across the three lung function groups, but now calibrate our models to match the observed annual 2016 costs from these analyses.</p> <p>All but one of the clinical trials used only the respiratory domain of the CFQ-R. In the one trial that evaluated the other domains of the CFQ-R there is some indication that there are quality of life improvements in the other domains. Unfortunately we don’t have a preference-weighted metric to use to model these effects. To evaluate the potential impact of this we performed an additional scenario analysis where we evaluated an independent effect on patient utility, varying it from 0 (no additional effect) to 0.05.</p>
5.	<p>Accredited cystic fibrosis care centers</p> <p>The cystic fibrosis Care Center Network is made of over 120 accredited care centers specializing in the treatment of CF. Nearly 85% of people with CF in the United States receive care at an accredited center. Care centers deliver multidisciplinary, evidence-based care, conduct clinical research, and maintain continuous quality improvement programs. This high-quality, specialized approach to care has improved survival for people</p>	<p>We incorporated the proportion of CF patients receiving care through the Care Center Network, as well as details on what these centers provide for patients. We also note that these centers have improved survival of CF patients for those able to receive care through the Network.</p>

	with CF. ¹ CF centers focus on addressing lung function, nutritional status, airway microbiology, and other comorbidities that affect survival. While coordinated multidisciplinary care has greatly improved mortality, clinical care alone has not been able to significantly affect morbidities such as reducing pulmonary exacerbations. Therefore, clinical care in addition to CFTR modulators provide people with CF the greatest opportunity for maintaining health. We recommend ICER include these points in the <i>Controversies and Uncertainties</i> section.	
6.	Identifying low value services We appreciate ICER’s interest in identifying low value services in CF care that arise from modulator treatment. Clinical guidelines developed by multidisciplinary and independent committees ² provide population-level guidance on respiratory, nutrition and GI, modulator use, and other areas of CF care. Modulator therapies are currently intended to complement existing best practices, but CF Patient Registry data shows that some standard-of-care therapies have been discontinued. To keep up with the evolving treatment landscape, randomized withdrawal studies are being planned to help inform possible changes to the current CF care regimen.	Thank you for your comment. We added mention of these planned studies to the revised report.
7.	Page 1, Pathogenesis: Clarify that while approximately 300 <i>CFTR</i> mutations have been fully characterized, the majority of the 1,800 mutations identified are known to be associated with a CF phenotype. Need to correct 7 th sentence: 87% of people with CF have at least one copy of the <i>F508del</i> mutation (these individuals may be heterozygous OR homozygous) and 46% of patients are homozygous for the <i>F508del</i> mutation (this is a subset of the 87%).	Thank you, we have added the suggested clarification about mutations associated with CF phenotype, and we have rewritten the sentence about the prevalence of <i>f508del</i> mutations.
8.	Page 2, Pathogenesis: Suggest revising “pulmonary toilet” to “pulmonary treatment.” <i>Streptococcus pneumoniae</i> is not an appropriate example when discussing initial infections that lead to CF pulmonary exacerbations.	We have changed the text to pulmonary hygiene. We have also deleted the reference to a specific pathogen.
9.	Page 3, Diagnosis: Clarify that early diagnosis leads to early treatment and therefore improved health outcomes; as written, the text neglects to connect early diagnosis and early treatment.	Thank you. We agree and have amended the text.
10.	Page 4, Management: Suggest adding “historically” to the beginning of the first paragraph. The addition of CFTR modulators to the CF treatment arsenal means clinicians are not solely trying to control symptoms, but rather are correcting basic protein defects causing symptoms. Suggest changing “chest physiotherapy” to “airway clearance” as this includes chest physiotherapy as well as commonly used airway clearance devices.	We have added the concept that controlling symptoms is the historic aim. We have added airway clearance devices, but maintain chest physiotherapy as a descriptor as well.

¹ Mogayzel, et Al. *Improving chronic care delivery and outcomes: the impact of the cystic fibrosis Care Center Network*. BMJ Qual Saf 2014 Apr; 23 Suppl 1:i3-8.

² Sponsored by the CF Foundation

11.	Page 5, CFTR modulator drugs: Sentence 4 should be edited to read “For example, patients who are homozygous for class I mutations cannot respond to modulator treatments because there is no CFTR protein to be modulated.”	Thank you. We agree and have amended the text.
12.	Page 8, Clinical outcomes: Pancreatitis and infertility are clinical manifestations of CF, but not common endpoints in clinical trials.	The list of outcomes of interest is not meant to be equivalent to the list of outcomes reported in studies. We have retained these outcomes as outcomes of interest.
13.	Page 9, adverse events: Sweat chloride and fecal elastase provide evidence that modulators are addressing the basic defect of CF; for what reason were these excluded?	These outcomes were not included because we did not evaluate whether the drugs address the basic defects of CF, but instead on their patient-centered clinical effects and harms. We have added a sentence to this effect.
14.	Page 12, Insights Gained: Suggest saying “airway clearance” rather than “airway hygiene.”	Thank you for your comment. We continue to feel that airway hygiene is the better term in this context, but added the term airway clearance in our description of the management of the condition.
15.	Page 15, Cystic Fibrosis Foundation guidelines: To help inform the standard of care delivered at accredited care centers, the CF Foundation brings together committees of subject matter experts to write guidelines on topics related to the care of people with cystic fibrosis. The Foundation acts as a facilitator for the development of guidelines and does not independently develop them.	We have added the suggested language for clarification of CFF guidelines.
16.	Page 15, Respiratory Care Guidelines: “Tobramycin” is misspelled. Dornase alfa is recommended for patients at all stages of the disease, not only individuals with severe disease.	Thank you for noting the typo, it has been corrected. We added that dornase alfa is recommended for patients at all stages of the disease.
17.	Page 16, Pulmonary Exacerbations: Guidelines recommend daily dosing of <i>intravenous</i> aminoglycosides during exacerbations. Further, in guidelines, “not recommended” is not equivalent to a decree that a certain treatment or treatment regimen is never indicated; it only alludes to a lack of evidence to make a formal recommendation. Home IV treatment is often used and is an important option in certain circumstances.	We made the correction about intravenous aminoglycosides, and included clarifying language about treatments that are not recommended.
18.	Page 29, Pulmonary Exacerbations: Regarding the KONNECTION study, as we mentioned in previous comments, 8 weeks is likely too short a timeframe to capture exacerbations.	We have added the short duration as a limitation to the study.
19.	Page 39, Table 3.8: Remove negative sign in -0.0.	Although technically correct, we agree this may be confusing. We have replaced this with a footnote stating the CI range is nonsignificant.
20.	Page 42, Clinical benefits of tezacaftor/ivacaftor in individuals heterozygous for the <i>F508del</i> mutation: To clarify, this title	Thank you for noting this. We have added text, in particular regarding the limitations,

	refers to individuals included in the clinical trial and differs from the FDA label indication. On the FDA label, tezacaftor/ivacaftor is indicated for individuals heterozygous for an indicated residual function mutation regardless of the second mutation.	that the reviewed evidence does not address all populations for whom the drug was approved.
21.	Page 49: Regarding day-to-day fluctuation in lung function, these factors should be equally distributed in a placebo-controlled trial across the arms and therefore should mitigate concerns about fluctuations. For patients that experienced lung function decline, it is difficult to be certain if an individual's decrease in lung function is causally related to the modulator or coincidental. Regarding the expansion of access to accredited CF care centers, clinical trials were conducted in many of the highest quality care centers, so it is unclear why an unanswered question about access to care centers being as impactful as modulator therapy is posed.	We have revised our description of the uncertainties regarding variability in FEV1 to reflect that these apply at the patient level and not at the larger population level. We've also clarified our description of uncertainties around equitable access to CF care and discussion on the effect of public insurance on survival, noting that the trials discussed showed improvements for patients at CF care centers assumed to be providing best supportive care.
22.	Page 56, Table 4.1: The assumption that best supportive care is the same in all treatment arms is questionable, especially in young patients, as this may underestimate the effect of early treatment and prevention of disease.	The trials did not report on what best supportive care entailed in detail, so it is difficult to model any differences. To the degree that CFTR modulator therapy prevents progression of lung function decline, patients will experience a lower burden of maintenance care.
23.	Page 57, Clinical Inputs: It is assumed that people with lung functions above 30% ppFEV ₁ have a 0% chance of lung transplantation, which is not true. Some individuals do receive a transplant with lung function above 30% ppFEV ₁ .	We based this assumption on the threshold for transplant cited in clinical guidelines. While it may be the case that some patients above this threshold do get a transplant, it is impossible to estimate what this rate would be without evidence.
24.	Page 76, Other Benefits: Per our comment letter, this section should be greatly expanded and note the long-term potential of modulating therapies, especially for children who begin treatment young.	Thank you for your comment. We have attempted to capture the long-term potential of modulating therapies in our model, but also note that long-term data on the durability of CFTR modulator effects is evolving and will continue to do so.

Sue Landgraf and Siri Vaeth, Cystic Fibrosis Research Inc.		
1.	<p>We cannot stress strongly enough the critical need to make life-changing CFTR-modulating therapies accessible to those who would benefit from them. The results of this report may provide justification to payers to refuse coverage of the cost of these therapies, increase the risk that they will be inaccessible to those who most need them, and ultimately discourage investment in and development of new drugs for the cystic fibrosis and rare disease community.</p> <p>Cystic fibrosis is still a fatal disease. Last year, half the individuals with CF who died were under 30 years old. And 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. For those with advanced lung disease, the fear of a catastrophic hemoptysis or pneumothorax is ever present. To conduct a cost-benefit analysis weighing the cost of each pulmonary exacerbation with the cost of the medications that significantly reduce exacerbations is patently insensitive and stunningly non-patient-centered. We have deep concern that your report will give credence to state and private payers who seek to reduce costs by keeping vital therapies out of the hands of those who would benefit from them.</p>	<p>Thank you for your comment. As we have stated above: rather than discouraging innovation, we feel that our mission is to produce rigorous examinations of the evidence that will lead to sustainable access to high value care for all patients. When prices are not aligned with value, this access is called into question.</p>
2.	<p>Tess and Victoria’s health challenges and complex medical regimen are very similar to many others with CF. In our decades of involvement with the cystic fibrosis community we have heard numerous tales of suffering and loss. We hear about people who have had to leave beloved careers due to declining health; young adults unable to live on their own due to their complex medical regimens; families repeatedly separated for weeks at a time due to hospitalizations; and of course, the excruciating pain of losing a child, sibling or spouse. Recently we lost several close members of our CF community who ranged in age from 12 years to 40 years. Our community needs options. It is imperative that individuals have access to new CFTR-modulating therapies. As the analysis of studies conducted by ICER shows, there is a range of responses to these therapies. Our fear is that a statistical analysis of costs versus benefits has completely stripped the human pain and suffering experienced by those diagnosed with CF and their loved ones out of the equation.</p>	<p>Thank you for your comment. We heard these same concerns in our conversations with multiple patients, caregivers, and patient advocacy groups. Though it is not possible to include every insight into our cost-effectiveness model, those quantitative assessments are only one part of our report. We focus considerable attention on the data available, its limitations, as well as highlighting key insights from all concerned groups, including patients and advocates, the purpose of which is to provide both our deliberating panel members and other stakeholders with the most well-rounded view possible of the disease, its treatment, and the challenges faced.</p>
Scott Grosse		
1.	<p>The ICER report used the Federal Supply Schedule (FSS) to determine discounted (net) prices of ivacaftor and lumacaftor/ivacaftor, which may be problematic. The draft report states, incorrectly, “The FSS supports the acquisition of pharmaceutical drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations.” The report may have confused the FSS price list established by GSA with the FSS program set up by the VA, which supports the acquisition of drugs and other products for the VA. The VA</p>	<p>We have reworded our description of the FSS to read: “The FSS is a price schedule set forth by the U.S. General Services Administration (GSA) that is used in negotiation with manufacturers of drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations.” While the FSS has limitations in determining actual price paid,</p>

	<p>program uses the GSA-negotiated FSS as a baseline but in addition negotiates further discounts, which are not publicly disclosed. The Congressional Budget Office in 2005 issued a report, “Prices for Brand-Name Drugs Under Selected Federal Programs” (https://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/64xx/doc6481/06-16-prescriptdrug.pdf), which documented actual payments by the VA and other federal health programs. On average, the CBO found that, taking confidential discounts into account, the FA paid 41% of the Average Wholesale Price for brand drugs.</p>	<p>we did not have other readily-available sources for net prices of these drugs.</p>
2.	<p>The assumed annual drug cost of ivacaftor is \$309,841.58. That is a reasonable approximation of the <u>gross</u> payment by private US payers but probably does not accurately reflect the magnitude of net payments. A 2017 report by the National Academies of Science, Engineering, and Medicine, “Making Medicines Affordable: A National Imperative” (https://www.nap.edu/catalog/24946/making-medicines-affordable-a-national-imperative), noted that on average manufacturers rebate to payers 28% of gross payments on branded prescription drugs.</p>	<p>While overall discounts on branded drugs have been cited as 27-28% on average, we note that this average discount is not generally reflective of the experience in orphan conditions with limited to no competition, where discounts are usually much lower.</p>
3.	<p>The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in 2010 sponsored a best practices guideline for calculating drug costs in societal-perspective cost-effectiveness analyses (CEAs), which was led by Joel Hay and published in <i>Value in Health</i> (https://www.ncbi.nlm.nih.gov/pubmed/19874571). The ISPOR committee proposed that prices of branded drugs be discounted by 40-80% as a proxy for the societal opportunity cost of drugs. I’m curious why ICER does not conduct sensitivity analyses on branded prescription drug prices using the ISPOR-recommended range.</p>	<p>We do perform threshold analyses on drug prices to suggest what an appropriate discount would be to achieve various cost-effectiveness thresholds, as shown in Table 4.14 in the report. As we considered the assumption of 40-80% discounts for these drugs to be an unrealistic base-case estimate in the current US environment, we refer to our scenario analysis as from a "modified societal perspective" (as suggested in the referenced Hay et al. article).</p>
4.	<p>The average treatment cost estimates for patients with cystic fibrosis (CF) derived from Lieu et al. (1999) are obsolete. They reflect treatment patterns at Kaiser Permanente of Northern California during 1996. Those estimates do not reflect the cost of “best supportive care,” which is defined on page 55 of the draft report. Best supportive care involves the administration of numerous pharmaceutical agents which were not on the market in 1996. In order to present valid estimates of the costs under the “best supportive care” comparator, it would be necessary to present estimates of treatment costs that include costs for currently used pharmaceutical agents other than the CFTR modulators.</p>	<p>We have updated the best supportive care treatment cost estimates to use more recent sources, as described in our report.</p>
5.	<p>The text on page 63 acknowledges that two published estimates of reimbursements for privately insured CF patients in fee-for-service plans (Ouyang et al. 2009; O’Sullivan et al. 2011) were substantially higher than the Kaiser Permanente study, even taking inflation into account. Regrettably, the report did not</p>	<p>Please see our response above to comment #4. Thank you for the comment and your permission to use the unpublished data cited here.</p>

	<p>acknowledge the magnitude of the differences. For example, the study by Ouyang et al. used MarketScan claims data and reported that expenditures per patient with CF enrolled in non-capitated plans during 2006 averaged \$48,100, with a median expenditure of \$30,500. In comparison, Lieu et al. reported mean and median 1996 costs of \$13,300 and \$5,300, respectively. The 2006 estimates are 4-6 times higher, which cannot be explained by inflation. The authors of the draft report presume that the difference reflects differences between health maintenance organization (HMO) and fee-for-service (FFS) plans. However, they offered no support for that assumption, which appears highly implausible. In 2016, the mean and median payments for CF patients under age 65 in non-capitated plans included in Truven Health MarketScan® Commercial research databases were \$126,600 and \$64,200, respectively (unpublished tabulation by commenter). The mean and median payments for patients enrolled in HMO plans (which comprised about 10% of the MarketScan Commercial sample enrollment) were \$140,000 and \$88,200, respectively (unpublished tabulation by commenter). The fact that estimated payments associated with care for patients with CF were even higher for HMOs than for non-capitated plans challenges the assumption that the low cost estimates reported by Lieu et al reflect a difference in payments between capitated and non-capitated plan types. That does not exclude the possibility that the cost structure may differ in an integrated health care system such as Kaiser Permanente, but it does suggest that one cannot generalize from the latter to other types of HMOs.</p>	
6.	<p>The report states, “Based on health insurance information reported in the 2016 CFFPR, we assumed a 60%/40% insurance mix (private/other) and applied a multiplier to our base estimates to model the higher private payer costs.” It appears that the analysts took the Lieu estimates from Kaiser Permanente as a proxy for costs by public payers. That assumption may not be justified; Kaiser Permanente is a low-cost provider but includes both public and private payers. The multiplier used to adjust for private payer costs based on the two other studies is not reported.</p>	<p>Please see our response above to comment #4.</p>
7.	<p>MarketScan Medicaid data can be used to estimate reimbursements, but Medicaid HMO data in many cases do not reflect patient costs. In 2016, mean and median payment for Medicaid FFS patients with CF in the MarketScan Medicaid sample averaged \$83,200, with a median of \$51,700 (unpublished tabulation by commenter). Medicaid HMO payments averaged \$49,100, with a median of \$9,900 (unpublished tabulation by commenter). A large percentage of the HMO enrollees with CF supposedly had \$0 annual costs, which can only be explained by cost data not being reported for them. That is why health services researchers generally use claims data from FFS or non-capitated plans rather than from fully capitated plans.</p>	<p>Please see our response above to comment #4. Thank you for the comment and your permission to use the unpublished data cited here.</p>

8.	<p>Since the mid-2000s, healthcare expenditures for CF have increased much faster than the general rate of medical inflation. An unpublished tabulation of MarketScan claims data for 2010 through 2016 found that the average annual rate of growth in per-patient spending for privately insured patients in non-capitated plans increased by 10.8% per year above the rate of general medical inflation. Even excluding spending on CFTR modulators, spending increased by 4.8% per year faster than general medical prices. Therefore, simply adjusting older CF cost estimates, even those of Ouyang et al. 2009 and O’Sullivan et al. 2011, for medical inflation will inevitably result in substantial underestimation of current treatment costs for insured patients with CF. The largest source of growth in healthcare costs in CF is the use of specialty medications that the draft report lists under best supportive care. In 2016, mean spending on pancreatic enzyme products and pulmonary specialty medications together amounted to more than \$27,000 per year per privately-insured CF patient in the MarketScan Commercial sample (unpublished tabulation by commenter).</p>	<p>Please see our response above to comment #4. Thank you for the comment and your permission to use the unpublished data cited here.</p>
9.	<p>The draft report inappropriately used the medical care component of the Consumer Price Index (CPI), which was developed to adjust out-of-pocket medical spending for inflation, to characterize inflation in overall medical costs. In an article published online in <i>Health Services Research</i> in November 2016 and in the March 2018 print issue of the journal, Dunn, Grosse, and Zuvekas (https://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+27873305) pointed out that the medical care CPI is appropriately used to adjust out-of-pocket costs but argued for the use of one of two unbiased measures of overall medical price inflation, the CMS Personal Health Care deflator and the BEA Personal Consumption Expenditures index for health by function. This is also explained on an Agency for Healthcare Research and Quality webpage: https://meps.ahrq.gov/about_meps/Price_Index.shtml.</p>	<p>We now update our costs using the Personal Health Care deflator. In general it lowered the magnitude of the cost increases. However, because we have updated the sources of many of our costs, our costs are now higher in absolute terms.</p>
<p>Juliana Keeping, Patients for Affordable Drugs</p>		
1.	<p>Limitations of ICER Framework</p> <p>The ICER value analysis is just one input that should be considered in arriving at the appropriate price for a new drug therapy. ICER does not address societal and ethical issues that are of the utmost importance for the health and well-being of patients and our nation.</p> <p>ICER does not consider the role of the patient community, taxpayers and government in the invention of new drugs. Because ICER does not consider appropriate returns for the drug manufacturer, it cannot take into account societal investment which reduces risk and should therefore reduce return to the company commercializing the drug.</p>	<p>We agree that our value-based price benchmarks and other economic analyses do not attempt to capture the role of public investment in drug development and is thus not designed to examine whether the drugmaker is receiving a “fair” return on investment in light of those contributions. Our approach is focused singularly on whether current pricing (however it is derived) is in alignment with clinical benefit to the patient, given current evidence.</p>

	<p>ICER does not consider what is an appropriate price based on the investment to develop, produce, and distribute a drug. Given limited societal funds and necessary trade-offs when scarce resources are directed to unwarranted profits, this is an element that should be taken into account when arriving at a price.</p>	
2.	<p>The Role of CFF Community Charitable Giving and Taxpayers</p> <p>Taxpayers and charitable donations paid for the foundational science for behind Kalydeco and Orkambi. The funding came from donations through the Cystic Fibrosis Foundation (CFF), which were tax deductible, and from the National Institutes of Health (NIH.) As mentioned above, Vertex bought the patents to the two drugs for a payment of \$3.3 billion.</p> <p>One argument for high prices is that investors must be compensated for the high risk involved in doing the basic scientific research and clinical trials to bring a drug to market. Without that incentive, they say, new life-saving treatments will not be invented and made available to people who need them.</p> <p>But in the case of Orkambi and Kalydeco, the CFF community and taxpayers took the risk, and Vertex moved to acquire the IP only after the treatments were shown to be viable. In fact, the New York Times reported “Cystic fibrosis was not a priority, and Vertex officials have said the program might have been dropped if the foundation had not been paying for it.” Thus, Vertex cannot lay claim to a return adjusted for high risk.</p>	<p>Thank you for raising these important points. While the costs and sources of funding for drug development are outside the realm of our framework for assessing value, they are important elements of the drug pricing discussion overall.</p>
3.	<p>Conclusion</p> <p>Orkambi and Kalydeco are priced too high according to ICER’s analysis. And Vertex’s profitability and executive compensation merely confirm that fact looking at the issue through another lens. Vertex does not deserve a high risk adjusted price as philanthropy and taxpayer-funded research lowered the risk for the company dramatically. Vertex is not using its windfall to invest in research, but rather to pay executives and buy back stock. It can easily lower the price to come in line with ICER’s findings.</p>	<p>Please see our response to comments 1 and 2 above.</p>
<p>Terry Wilcox, Patients Rising NOW</p>		
1.	<p>As an initial comment, we again want to recognize that while ICER’s reports assert that they represent the best interests of all stakeholders, (“All stakeholders will therefore benefit from a comprehensive review of the clinical evidence and potential economic impact...”), but we (and many others), continue to find that the intended audience for ICER’s work is payers in the United States – which is reflected in the Midwest CEPAC Advisory Board’s composition. ICER’s approach is clearly contrary to the conclusions of leading health services researchers and economists who have stated that “No single</p>	<p>We feel that our framework is structured to reflect the views and perspectives of multiple stakeholders. In addition, because a review of data alone cannot begin to address the full lived experience of patients, we separately seek input from patients and patient groups to understand the nuances associated with disease and treatment. We also seek to identify key populations of patients that may benefit more (or less)</p>

	<p>perspective can represent the interests of all participants in value-based decisions.” We concur that analyses and conclusions claiming to represent all stakeholders are both analytically hobbled and inconsistent with the reality of the U.S.’s multi-payer system that covers different sub-populations.</p>	<p>from treatment, but note that evidence on such sub-populations is often unavailable.</p>
2.	<p>ICER’s Process for Ultra Rare Conditions We appreciate ICER developing modifications to its framework for ultra-rare diseases. As is widely recognized, health care delivery, development of diagnostics and treatments, reimbursement practices, and health care policy and administration are rapidly evolving in a connected way in response to scientific advancements that are driving precision and genomic medicine. As more diseases are divided into genetic subpopulations, the number of people with unique diseases continues to grow. Thus, while ICER’s cut-off of 10,000 people in the United States seems like a reasonable number for defining the term “ultra-rare,” we believe the process of analyzing the importance (to use a word other than “value”) of therapeutic options for patients should be approached as a continuum recognizing the characteristics of each clinical condition, the population affected, the implications of that condition for different payers (based upon the populations they cover), and above all, the range of patient’s perspectives about needs and goals.</p>	<p>As we have noted in the development of our ultra-rare adaptation, conditions at the higher prevalence end of what regulators might consider “rare” (e.g., 200,000 individuals as defined by the FDA) do not suffer from the same challenges in clinical trial recruitment, use of standard and validated outcome measures, and other related concerns in comparison to rarer diseases. We felt that the ultra-rare threshold we use represents a reasonable compromise toward identifying a set of conditions with challenges regarding evidence generation and incentives for innovation.</p>
3.	<p>ICER’s analysis in the draft evidence report particularly fails to adequately consider two related aspects important to patients: real option value, and the spillover effect on research and development (R&D). Those elements of value described by Garrison et al. are critically important to patients with serious and life-threatening conditions but are not adequately considered in ICER’s draft evidence report. Concerning, real option value, ICER fails to recognize the importance to patients of extending life with reasonable function and quality of life so that they are able to take advantage of new treatments that will become available in the future and that may dramatically improve their health and wellbeing. We noted in our comments concerning hemophilia treatments that this was certainly the case for people with AIDS in the early 1990s, and we assert that it is the rule, not the exception.</p>	<p>While Garrison et al. (in <i>Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis</i>) have recently proposed the use of expanded value frameworks incorporating a wider range of values (including option value and spillover effects), they have not historically been standard elements of cost-effectiveness analyses, and more methodologic research and data are needed before their standard inclusion. In fact, Garrison et al. also note that: “Further thought and research are needed on how best to measure and integrate these elements into an incremental value framework and on coverage and pricing decisions.”</p>
4.	<p>And concerning what Garrison et al. term “spillover effect” for R&D, we recognize that how payers, regulators, and others reimburse, enable or limit access, and otherwise manage (or manipulate) access to treatments (including all clinical services, diagnostics, and therapeutics), sends a very direct and strong signal (or “alert”) about priorities for R&D work and investments. As ICER clearly recognizes that overall health spending is not a bottomless pot, the situation is the same for R&D and care delivery investments. That is, choosing which</p>	<p>We agree that resource allocation decisions around R&D and care delivery may be influenced by access and funding decisions, but the magnitude of these impacts in any particular case is not readily discernible. Nor is it clear how these impacts could be reflected in the assessment of particular treatments currently being considered for funding.</p>

	diseases and conditions to build clinics for, develop diagnostics for clinicians to use, and create new therapies to help patients, are all decisions made one against another within the context of scientific, clinical, and financial knowledge and opportunities.	
5.	We also believe that any value analysis (by ICER or others) that includes patient perspectives should explore actual patient costs. We recognize that understanding the pluralistic system of private and public payers in the U.S. and how the resulting system of rebates, discounts, and other factors influencing patient costs and access is not a simple analysis. However, it is our understanding that this is one of Dr. Pearson’s areas of expertise since he has provided insights to at least one major pharmacy management company (i.e. Express Scripts), for their oncology value care program. Therefore, we would expect ICER to be able to attempt to include aspects of those activities for patients in its work and publications, e.g., by developing a formula for the estimation of rebates as part of ICER’s economic methodology. It is only with such broader cost analyses that progress can be made towards more patient-centered value-based care.	Out-of-pocket costs vary greatly across payers and plans, and there is no way to reliably estimate these costs. In addition, the data required to conduct such analyses are almost always confidential. While we agree that actual patient costs are of the utmost importance to patients, we have no way to reliably determine them.
6.	An additional aspect of patient perspectives that we want to raise – and would hope would be discussed at the May 17th Public Meeting – is the reliance on the respiratory domain scores of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) patient survey instrument. As the draft evidence report states, the “CFQ-R measures quality of life and physical disease symptoms using the following scales: physical functioning, emotional functioning, social functioning, body image, eating problems, treatment burden, respiratory symptoms, and digestive symptoms.” We recognize that we are not experts in this area of clinical research, and understand that ICER “primarily focuses on the CFQ-R respiratory domain score since it was reported in the pivotal trials of the CFTR modulators.” However, given that that the survey instrument does include other components that may also be very important to patients and their families, we would appreciate ICER (and others) exploring how to more equitably incorporate data from those components into analyses of value. Just as the FDA (and others) are looking to expand how they use patient reported outcomes in their work, we would hope that ICER would similarly strive to be expansive in incorporating all types of patient focused data, and not just that which is most statistically significant or medically significant, but rather what is most significant to patients.	<p>We agree that data on CFQ-R domains other than the respiratory symptoms were limited, and that as a result, quality of life may be incompletely captured. When available, we reported data from all domains, however, we found only one publication including domains other than respiratory symptoms, as presented in the draft and revised reports.</p> <p>For the economic analyses, we only had utility data on lung function and not on other domains. Unfortunately, the CFQ-R, which indicates that there may be improvements in other domains, does not translate directly to an improvement in utility. To examine this potential effect, we now provide a scenario analysis where we allow an independent increase in an individual’s utility.</p>
7.	Therefore, we strongly urge that those aspects of value important to patients be given considerable discussion at the May 17th Public Meeting and during the voting by the Midwest CEPAC – and specifically related to final question under Contextual Considerations, i.e., “There are additional contextual considerations that should have an important role in judgments	We agree with this comment, and we plan to spend a significant portion of the May 17 Public Meeting discussing aspects of value important to patients, as well as discussing and voting on the Other Benefits and Contextual Considerations section of the report.

	<p>of the value of this intervention: _____.”</p>	
8.	<p>And finally, in our experience, many patients living with chronic and life-threatening illnesses develop an advanced scientific and practical clinical knowledge in their specific disease, and thus are experts in its impact for their body and life. This is especially true for the parents of younger patients, such as those with CF. And yet, those vital voices of value have only apparently been included as secondary sources sought for comment, and are absent from the voting panel that will be considering critical aspects of ICER’s work at the May 17th meeting, with only one pediatrician on the CEPAC Council and no pulmonologists. We find this ongoing selection bias for patient perspectives a serious and significant problem with ICER’s process, and do not understand how ICER’s voting process – particularly related to “contextual considerations” – can responsibly occur without the direct participation of affected patients and families.</p>	<p>We disagree with this characterization of our patient engagement process. For each review, we seek out input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including calls with patients and patient advocacy organizations at the beginning of each review to learn which outcomes are most important from their perspective. We also invite patient advocacy groups to review early drafts of our report. In addition, we invite patients with the condition under review to participate in our public meetings through both oral comments and formal participation throughout the meeting as part of a policy roundtable.</p> <p>The voting panels at ICER’s public meetings are composed of patient/consumer representatives, clinicians, and health policy researchers with broad expertise in evaluating evidence on clinical effectiveness and comparative value. We have purposefully recruited the panel membership for a diversity in experience and background to ensure the objectivity of the deliberations at the meeting.</p>
9.	<p>QALYs We have previously expressed our concern about ICER’s use of QALYs, but ICER’s approach to the use of QALYs has not significantly changed, thus we feel the need to revisit the issues. Specifically, since QALYs were developed solely for economic analysis (and to enable rationing in the UK’s National Health Service) using QALYs as the core of value assessments is a very un-patient centered analytical construct. In this vein, we share the CF Foundation’s “concerns about the use of quality-adjusted life-years (QALY) as the primary measure of the cost-effectiveness analysis as QALYs do not account for patient-reported outcomes.”</p> <p>Overall, Patients Rising Now supports systematic cost effectiveness evaluations as part of determining value for patients – as long as it is done in a transparent and responsible manner. That is, all value frameworks and assessments should be conducted using an evidence-based, patient-centered</p>	<p>We appreciate your concerns about relying on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues you raise are part of the Other Benefits and Contextual Considerations section, which are essential in a full consideration of value.</p>

	<p>approaches based in science, eschewing ideological bias, and explicitly recognizing the intended uses and decision makers. Unfortunately, we continue to find that ICER's work does not meet those standards.</p>	
<p>10.</p>	<p>Budget Impact</p> <p>We would also like to revisit some aspects of our comment letter on ICER's draft evidence report about hemophilia given ICER's response to those comments. Specifically, we appreciate ICER's response – and agreement – about the importance of recognizing the uneven distribution across payers and health care delivery systems of patients for conditions like hemophilia. As ICER itself noted in responding to our previous comments, "We appreciate the desire to make ICER's budget impact analyses as granular and relevant as possible for "individual health programs, payers, or groups of patients." However, in a fragmented health care system such as that in the United States, the multiplicity of payers, provider organizations, and state and federal health programs would make such an exercise a major undertaking in itself, and would require the collection of data unique to each organization (and in some cases proprietary to those organizations). We believe that each of these organizations is better suited to judge the budgetary implications of new interventions for their particular populations and settings."</p> <p>While ICER's position seems to be that doing this multi-party analysis would be hard, we would argue that while only doing a national level analysis as if the U.S. had a single payer health system is certainly easier, but just because something is hard is not an excuse for doing something else that is easier and misleading, particularly because many, many other analytical organizations do evaluations of individual health systems, care practices, or payers all the time. So why can't ICER? Presumably for the same reason that it repeatedly compares itself to government agencies or organizations in other countries, i.e., ICER continues to view itself as acting as (or on behalf of) an agency of the Federal government that is running an illusory uniform U.S. health care system.</p>	<p>As noted above, costs and benefit structures vary greatly across payers and plans in the United States, and there is no way to reliably estimate these costs without data at the level of individual plans. In addition, the data required to conduct such analyses are often confidential, making these analyses not only difficult but impossible. Specific payers routinely conduct their own budget impact analyses (or modify analyses provided by manufacturers or consultants) using data specific to their own populations and settings.</p> <p>That said, we believe that a national-level budget impact analysis is useful to decision-makers, by raising alerts if the impact on a national level is likely to lead to growth in overall costs that may require additional steps to manage access and sustainability.</p>