BOOMER ESIASON FOUNDATION

Response to the ICER Draft Evidence Report on CFTR Modulators

As a follow up to my letter, dated November 17, 2017, and in response to the recent ICER draft report, I'd like to share my concerns.

I have concerns that the draft evidence report does not share the complete picture of the value of these medicines to those living with cystic fibrosis, such as my son, Gunnar.

CF is a deadly, progressive disease and those living with CF have a projected life expectancy of 40 years. Patients living with CF must endure hours of therapy and take dozens of medicines each day just to stay healthy. And, their version of staying healthy means not spending weeks at a time in the hospital. Their "healthy" is not typical. Breathing is a challenge every day.

CFTR modulators are innovative medicines that have changed the course of CF and have given hope to thousands across the country. But the medicines available today help only half of all CF patients that have certain mutations. Patients like Gunnar are still awaiting a treatment. How can we not provide opportunities for all CF patients to live a full life? They need choices among treatments as the variability of success is not "one size fits all."

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.

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.

Today, Gunnar is a successful 27-year old young man. I'm hopeful that he'll live for many more years to come. Please help us move closer to this being a reality, not further.

Warmest Regards,

Boomer Esiason, Chairman

CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

April 12, 2018

Steven Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Evidence Report

Dear Dr. Pearson,

On behalf of the 30,000 individuals living with cystic fibrosis (CF) in the United States, we write to provide public comment on the *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Evidence Report.* These disease-modifying therapies are transformational and represent tremendous potential to alter the course of cystic fibrosis. We are pleased to see the report incorporates several important points of feedback we provided throughout the development of the report. We look forward to further improvements following this public comment period, particularly better characterizing the potential benefit of long-term modulator use, the impact of this chronic life-threatening disease on daily life, and the limitations of the model in capturing the complexity and heterogeneity of CF.

Potential benefits from long-term and early initiation of CFTR modulators

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 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 *CFTR* 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.

Differences between lumacaftor/ivacaftor and tezacaftor/ivacaftor

The draft evidence report notes that for individuals with two copies of the *F508del* 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.

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 *CFTR* 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:

- Use of clinical trial participation criteria to justify coverage exclusions: public and private payers cite lack 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;
- 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.

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.

Model limitations

We are pleased to see the initial economic model has been revised to include both $ppFEV_1$ 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 $ppFEV_1$ 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.

Accredited cystic fibrosis care centers

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 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 *Controversies and Uncertainties* section.

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 again for the opportunity to comment on the draft report. Please note that we have included some line edit suggestions in an appendix to this letter. We look forward to the revised report and discussion at the public meeting in May.

Thank you,

Preston W. Campbell, III, MD
President and Chief Executive Officer

[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

Appendix

Page 1, Pathogenesis: Clarify that while approximately 300 *CFTR* 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 7th sentence: 87% of people with CF have at least one copy of the *F508del* mutation (these individuals may be heterozygous OR homozygous) and 46% of patients are homozygous for the *F508del* mutation (this is a subset of the 87%).

Page 2, Pathogenesis: Suggest revising "pulmonary toilet" to "pulmonary treatment." *Streptococcus pneumoniae* is not an appropriate example when discussing initial infections that lead to CF pulmonary exacerbations.

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.

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.

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."

Page 8, Clinical outcomes: Pancreatitis and infertility are clinical manifestations of CF, but not common endpoints in clinical trials.

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?

Page 12, Insights Gained: Suggest saying "airway clearance" rather than "airway hygiene."

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.

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.

Page 16, Pulmonary Exacerbations: Guidelines recommend daily dosing of *intravenous* 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.

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.

Page 39, Table 3.8: Remove negative sign in -0.0.

Page 42, Clinical benefits of tezacaftor/ivacaftor in individuals heterozygous for the *F508del* mutation: To clarify, this title 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.

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.

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.

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% $ppFEV_1$.

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.

April 11, 2018

Institute for Clinical and Economic Review
Midwest Comparative Effects Public Advisory Council
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Members of the Institute for Clinical and Economic Review,

We write to submit our comments regarding the draft Evidence Report "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value," assessing the comparative clinical effectiveness and value of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Our perspectives on this topic are personal and professional: we are both mothers of young women with cystic fibrosis (CF), and we are, respectively, the Executive Director and Associate Director of CFRI, one of the largest nonprofit community-based cystic fibrosis organizations in the country. We work directly with members of the CF community from across the United States, and as such have broad input on the positive impact that CFTR-modulating therapies are having on the lives of those whose CFTR mutations are responsive to these therapies. We are also active in advocacy to ensure access to therapies and care, and are very concerned by the report's analysis. 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.

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.

CFRI has over 17,000 constituents. Our mission is to fund research, provide education and personal support, and spread awareness of cystic fibrosis to those living with and affected by the disease. All programs are offered to the nationwide CF community. CFRI provides educational and psychosocial support programs and services, advocates on the state and federal level for increased access to quality health care and affordable medications, and provides research awards for basic science CF research projects at academic institutions nationwide. Both of us have been involved with the organization for over 20 years.

Please allow us to share our personal experiences with this disease. Our daughters are ten years apart, and have had very different CF paths, possibly – and very likely – due to CFTR modulating therapies. Three years ago, Sue's daughter, Victoria, experienced sudden respiratory failure was put on life support, and was saved at the last possible moment by a double lung transplant. Two years ago, Siri's daughter, Tess, who is homozygous for the F508del mutation, began taking Orkambi, with extremely positive results. As Victoria copes with CF and rigorous post-transplant care, she and Sue have frequently pondered how her life might be very different today if these medications had been available just a year earlier.

Victoria was diagnosed with CF at the age of 22 months, and experienced unexpected liver failure and liver transplantation at age 12. In 2015, Victoria developed what she thought was a cold. Four days later she was in the intensive care unit, where she experienced respiratory failure and was placed on life support. While amazingly she was able to be extubated, her health and lungs were so severely compromised, that she could not leave the hospital without new lungs. She was in intense physical and emotional pain, suffering a severe hemoptysis that required embolization, and repeated lung bleeds. She again went into respiratory crisis, and at that critical moment, her doctors announced that they had accepted lungs for her. After a harrowing 36 hours, Sue's daughter received her new set of lungs. Only then did the doctor share with Sue that without transplantation, Victoria would not have survived another day.

While a double lung transplant was the only option to prolong Victoria's life, this has been accompanied by its own complex challenges. The surgery and recovery were brutal and painful. Victoria must now follow another highly complex regimen of immunosuppressant drugs that make her extraordinarily vulnerable to infection and the development of cancer. She lives with a daily fear of rejection, knowing that only half of those who receive a double lung transplant are alive after five years. And she still has cystic fibrosis with its multi-systemic impacts.

Siri's daughter Tess was diagnosed with cystic fibrosis at five months old, when in addition to her extreme failure to thrive she developed pneumonia. She has feared for Tess' survival since that day in 1995. Tess has had multiple hospitalizations for exacerbations caused by damaging lung infections, five sinus surgeries, and countless PICC-line placements for multi-week home IV antibiotics treatments. She takes nearly 50 pills per day, injects insulin to manage her CF-related diabetes, and spends a minimum of three hours per day doing respiratory therapy. She is a warrior, powering her way through the physical challenges to pursue her life goals. Through the years she has missed countless classes, performances and family events due to her disease. It has been extremely difficult to watch the physical and emotional pain and suffering she has experienced through the years.

Slightly less than two years ago, Tess began taking Orkambi (lumacaftor/ivacaftor). Since that time, she has maintained her lung function, has had no exacerbations, has not been hospitalized, and has had no need for IV antibiotics. How does one put a price on the preservation of her health? How does one quantify the value of her life? What is the value of her improved quality of life? While one can conduct a cost-benefit ratio analysis of the savings from avoiding hospitalizations versus the cost of the drug, this removes humanity from the equation. Our concern is that our daughters – and all others with CF - have an improved quality of life and are able to survive this cruel and debilitating disease with as little pain and suffering possible.

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.

Life with CF is a daily battle to slow the disease's progression. Prior to the arrival of CFTR-modulating therapies, no matter how adherent one was to the time-consuming daily CF medical regimen, the decline in lung function was inevitable. The line on the graph only trended steadily downward. The CF community must maintain a difficult balance between optimism and fear, hope and grief. The arrival of the first CFTR-modulating therapies has brought realistic hope that the downward course of the disease can be halted. It is a tragedy that for many – either due to their specific CFTR mutation or lung disease that is too advanced – these therapies are not an option. It would be an equal tragedy and travesty if the draft Evidence Report was used to deny access to these medications to those individuals who would benefit from them solely due to cost.

We know all too well that cystic fibrosis is an extremely capricious disease, and that an individual's health status can rapidly spiral out of control. Cystic fibrosis must be treated aggressively and early. It is imperative that cost not be a barrier to access to these life-saving therapies.

Our experiences with our daughters, and our work with the CF community impel us to express our strong concerns about this draft report. Cystic fibrosis is a rare disease. It is challenging to entice investment in new therapies. This report has the potential to justify payers to discontinue coverage, suppress research, and discourage investment in new drug discovery and development. This would be catastrophic for the cystic fibrosis community, and has broader implications for other rare disease groups.

Sue Landgraf
CFRI Executive Director

Siri Vaeth
CFRI Associate Director

To Whom It May Concern,

Thank you for taking the time to put together such a comprehensive report on the effectiveness and value of modulator treatments for Cystic Fibrosis. For all the data and analysis that went into this report the one thing that cannot be quantified is the impact of these drugs on the individual person, their family and the improvement in the quality of their day to day life.

My name is Chad Riedy and I am currently 36, married with two boys (7 and 4), and work full time. I currently spend two to three hours a day on treatments to stay healthy and that does not include exercise, managing prescriptions or cleaning equipment, all time that is not spent with family and friends.

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. For a good portion of my life we did not have therapies like hypertonic saline, inhaled antibiotics, or the vest and have seen firsthand how theses therapies have changed the way cf is treated and the difference they have made. 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.

Being homozygous for the F508del mutation, in the spring of 2013, I was able to participate in the Phase 3 and rollover study for lumacaftor/ivacaftor. For a little more than a year, while not knowing if I was receiving lumacaftor/ivacaftor (turns out I was receiving it) I noticed that even though I had not had an increase in lung function, I was rarely coughing, was not experiencing chronic sinus issues and had many more good days than bad ones. Unfortunately, due to an exacerbation that caused my lung function to drop from the low 40's to the low 20's over the period of six to eight months, coupled with increased chest tightness I had to stop lumacaftor/ivacaftor. In addition to stopping the drug that I had been waiting for and that gave me so much hope I started to discuss the possibility of a lung transplant. Hope quickly changed to fear and uncertainty.

Thankfully, in the Spring of 2015, my lung function stopped falling, rose slightly and eventually stabilized in the upper 20's and low 30's, where, for the past three years it has stayed, until recently.

In January of this year, I got a second chance to try the latest CFTR modulator, tezacaftor/ivacaftor, through an early access program. As my lung function was too low to participate in the different studies, I had to wait for word that it would be submitted for approval by the Food and Drug Administration. Within one month of being giving access, I saw my lung function increase by 5 percent. While this may not seem like a lot to some and when evaluated against the cost of this drug probably seems insignificant and not a cost effective method to treat cf. But when your lung function is at 28 percent, that 5 percent is the difference between being able to carry your kids up the stairs to bed at night or carrying them around when they are tired, and not being able to do so. It is the difference of being able to perform normal responsibilities of being a father and a husband.

In addition, the frequency in which I have anxiety and panic attacks in the normal flow of daily activities has been reduced leading to increased exercise, more playing with my kids and a desire to do the activities that I have hesitated doing for the past several years.

While taking tezacaftor/ivacaftor over the past three months has not lessened the amount of time I still have to spend on treatments and other cf related activities, it has provided a better quality of life right now and real hope for the days to come. Hope that with decreased exacerbations and lung function deterioration I will be able to grow old and gray with my wife, see my boys grow up and have many more days enjoying life.

These impacts my not generate the type of data that can help to justify the cost of these medicines on paper, they are real and to those of us and our families living with the harsh realities of this disease they are just as important.

Thank you so much for your time.

Sincerely,
Chad Riedy

To whom it may concern,

My son's current life expectancy is 47 years old. Major was born with Cystic Fibrosis in July of 2015. In a twist of fate, it was brought to our attention by our Pulmonologist, the same day Major was diagnosed, that Kalydeko had just been approved for public use.

Since that time, other drugs like Orkambi and Symdeko have been made available to the CF community. These are drugs that have given the CF population hope for a better future. A future for adults and children alike. In the short time that these drugs have been in the marketplace, the life expectancy has risen from 41 to 47. And we still don't truly know how much of a positive effect they could have over the course of years, decades, and lifetimes.

But we do know that these drugs have made lifetimes possible for people with Cystic Fibrosis. My son, Major, now has the chance to one day be what it is he dreams of. He doesn't have to have limits on who he wants to be or what he wants to do with his life. He could be a scientist, doctor, or attorney. Prior to these drugs, we would just have hoped that he would be a young adult. To Major and the rest of the CF population, drugs like Kalydeko, Orkambi, and Symdeko are priceless. Because no price can be put on the opportunity to live a full and productive life.

Sincerely,
Drew Strube, father

April 4, 2018

Steven Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Steven Pearson,

My name is Emily Kramer-Golinkoff. I am 33 years old with advanced-stage Cystic Fibrosis (CF) and co-founder of Emily's Entourage, a 501(c)3 that accelerates research and drug development for nonsense mutations of CF. I had the honor of being named a White House Precision Medicine "Champion of Change" on behalf of my work for Emily's Entourage.

I am reaching out to share my story for public comment on the *Modulator Treatments for Cystic Fibrosis: Effectiveness and Value Draft Evidence Report.*

In the past few years, game-changing new FDA-approved CFTR modulating therapies have translated hope into reality for many individuals with CF. I have watched with sheer awe as many of my CF friends with G551D, two copies of F508del, and other on label mutations started taking a single pill twice a day that allowed them to run marathons, start families, get off lung transplant lists, return to work, and plan for a future that they could actually believe in.

Unfortunately, with two copies of a nonsense CFTR mutation, I belong to the roughly 50% of the CF population for whom there are no approved CFTR modulators. My nonsense mutation compatriots and I are watching from the sidelines with happiness for our CF friends as they cross over to the other side of possibility, and with envy too. All we want is the chance to join them.

With advanced stage disease (35% FEV1), I can attest to the urgency of time for people with CF. With each passing week, month and year, we lose precious lung function that takes away our ability to live long, quality and productive lives with the people we love. Therapies like Kalydeco, Orkambi and Symdeko are the wishes we make as we blow our candles out each year.

Those wishes depends not only on continued medical research, drug development and innovation, but on time too. Those of us with advanced-stage disease do not have time to waste. I urge you to consider that our lives depend on innovation and, crucially, time is of the essence.

In addition, I implore you to talk to many diverse patients, families, and advocacy organizations to truly capture the whole CF voice and the life-changing impact of these therapies from those on the front lines.

Sincerely,

Emily Kramer-Golinkoff, MBE
Co-Founder, Emily's Entourage

To Whom It May Concern:

My son, Major Strube, was born in 2014. At the time of his birth, the life expectancy for a person with cystic fibrosis was around 40. At the time of his birth, that statistic had no impact on my life.

Within hours of his birth, I knew something was wrong. He wasn't eating well, he wasn't soiling his diapers, and he was spitting up a lot. Over the next 24 hours, the hospital staff grew increasingly worried. I knew we were headed to the NICU hours before I was actually told that by a physician.

CT scans indicated that Major had meconium ileus, an almost sure sign of cystic fibrosis. In an instant, my entire world shattered. I shook. I cried. I was inconsolable. Suddenly the life expectancy not only impacted my life, it defined my sons. I'd read a book about CF as a teenager and knew how devastating the disease was. I was heartbroken and already mourning the loss of the child I thought I'd have.

Despite my sadness, I jumped into learning about the disease from within the walls of the NICU. When the diagnosis was finally confirmed a few days later, something very special happened. Our team of doctors came in one by one with their take on the news. From each of them, I heard increasingly positive outlooks for cystic fibrosis. I was informed that research and drug development had grown leaps and bounds since I'd read that book as a teen. The life expectancy had almost doubled since then, and Major had a real shot of living to 40 and beyond.

That wasn't good enough, but it was a start.

Over the past 3 years, drug development has continued to grow at speeds I'm amazed by, and the safety and efficacy has done the same. Thanks to modulator drugs such as Orkambi, Kalydeco, and Symdeko, my son can dream of being a grandfather. I've seen the positive impact that the medications have had on other children with CF, other adults with CF, and I'm hopeful. I have hope that I wish I could show the old me. The me that was crying in the hospital hallway after hearing the CF diagnosis.

Because of modulators like the above, I believe Major will outlive me. I believe Major will be a grandfather if he chooses. I believe Major will be whatever he wants to be, thanks to science.

Sincerely,
Jaclyn Strube
Mother of a Child with Cystic Fibrosis

Comments of Juliana Keeping
Mother of Cystic Fibrosis Patient Eli, 5 years old

In Response to the Institute for Clinical and Economic Review
Draft Evidence Report on CFTR Modulator Therapies for Cystic Fibrosis

April 12, 2018

Background

My name is Juliana Keeping. My son, Eli, is 5 years old. He has the most common form of cystic fibrosis, with two copies of the Deltaf508 mutation. He takes digestive enzymes, vitamins, an inhaled breathing treatment called Pulmozyme, albuterol, saline and an antacid to maintain his health, along with doing one hour minimum of physical therapy per day for his lungs. During inevitable lung infections that are a part of living with this disease, he needs antibiotics and steroids. His long-term health and survival depends on Orkambi or future versions of this drug. Without new innovations in medicine, he will die.

Orkambi retails for $327,000; Eli will qualify for this drug in 2019. We have good health care insurance, but for much less expensive medicines, must depend on patient assistance programs to pay our share of the drug cost. We live in fear of further price increases or— God forbid—losing health coverage at some point.

I am proud to serve as Communications Director for Patients For Affordable Drugs (P4AD.) It is the only national patient organization focused exclusively on policies to lower drug prices. P4AD does not accept funding from any organizations that profit from the development or distribution of prescription drugs. I am also active as a supporter of the Cystic Fibrosis Foundation that funded early scientific research that led to these drugs, and which received a payment of $3.3 billion from Vertex when it acquired the rights to commercialize the drugs. I have raised more than $90,000 in grants and individual donations for the CF Foundation in Eli's first 5 years of life! I also met with Vertex executives to protest the prices of these drugs, and I have participated in shareholder meetings to encourage responsible pricing.

Value-Based Pricing and ICER Process

Right now, prescription drugs are priced without regard to the value they deliver to patients. Instead, corporations price their drugs based on maximizing profits. Value-based pricing for prescription drugs holds great promise as a framework that can move us away from pricing based only on the market power of drug corporations. Instead, we believe value should be the starting point for negotiations with government, employers, insurers, and other payers.

The work of the Institute for Clinical and Economic Review (ICER) can be foundational to the creation of a new system to ensure that patients have access to drugs they need and that those

drugs are accessible, affordable, and fairly priced. We applaud ICER for its work and for its inclusive and responsive process which engages patients and their families, listens to concerns, and takes into account our real world experience.

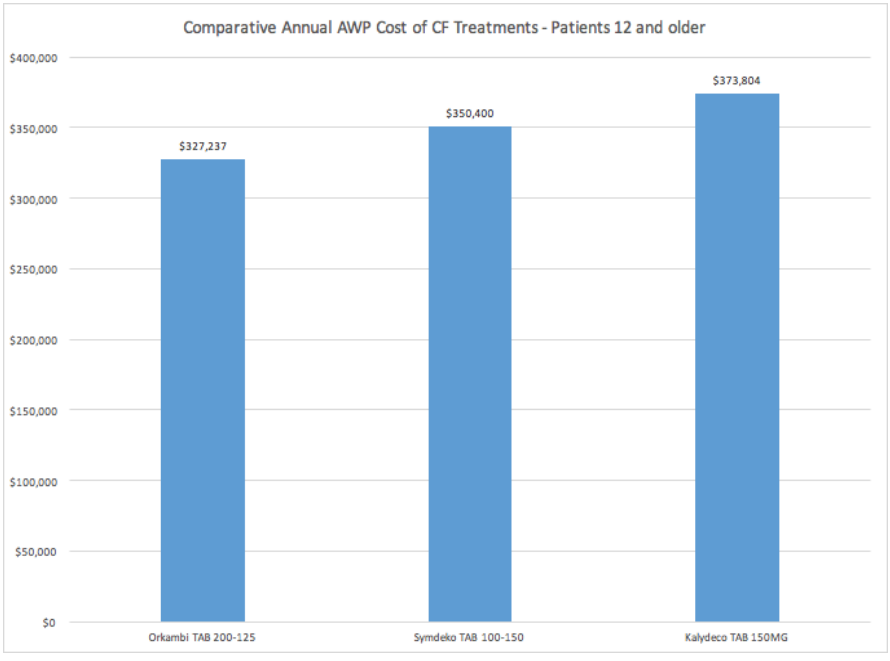
Limitations of ICER Framework

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.

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.

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.

The Prices of Orkambi and Kalydeco Are Simply Too High



Orkambi costs $327,000 and Kalydeco $384,000 per year, per the Healthcare data firm Connecture. A third Vertex drug, Symdeko, was not included in the ICER analysis but included in the graphic, and costs $350,000 per year. Since long before the ICER analysis, I have believed the prices are way too high. The price of the drug has been criticized since its introduction.We note that ICER found that the price of the drugs "would need to be reduced by about half to be considered cost effective," and we don't quarrel with that conclusion. My reasons for concluding the prices are too high are different from—and yet complement—the ICER analysis.

The Role of CFF Community Charitable Giving and Taxpayers

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.

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.

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.

Vertex Is Exploiting Its Monopoly To Gouge Patients and Payers

Vertex claims it needs to charge these prices to "continue to invest" in new drugs. But instead of investing in innovation, Vertex is buying back its own stock and bragging about having too much cash.

On March 13, 2018, Vertex CEO Jeffrey Leiden bragged 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." The company recently re-purchased $500 million of its own stock, enriching investors and failing to fund research.

Vertex's behavior is consistent with findings published in the Journal of the American Medical Association in August 2016 that "There is no evidence of an association between research and development costs and prices; rather, prescription drugs are priced in the United States primarily on the basis of what the market will bear." Truer words could not be spoken about Vertex pricing for these drugs.

Vertex Executives Have a History of Ethically Challenged Behavior

In 2012, Vertex misrepresented clinical trial results, leading to an increase in its stock price. At least half a dozen Vertex executives took advantage of the inflated price to cash in $100 million in stock options before revealing the true trial data, which were less positive.

CEO Jeffrey Leiden himself is making a killing at the expense of patients and other payers. His compensation has been condemned by groups like the corporate governance watchdog, Institutional Shareholder Services (ISS), which called the pay "excessive" and not based on rigorous performance metrics. In 2017 alone, Mr. Leiden's compensation was $78.5 million according to Axios.

Vertex has refused to provide compassionate use medication to patients on Medicaid. Four patients experienced life-threatening delays to the CF-funded drug Kalydeco as Arkansas struggled with the cost of the drug. The patients were forced to sue the state in 2014 and received no medicine on compassionate use grounds during the Medicaid appeals process or lawsuit. During this time, the patients grew gravely ill. Their doctors begged Vertex for medicine, to no avail. Nearly half of people with cystic fibrosis receive some form of Medicaid. In 2014, the same year CF patients, including a young child, suffered while being forced to fight for their medicines, Vertex CEO Jeffrey Leiden received a $46 million compensation package.

With specialty drug spending in the U.S. projected to balloon to $400 billion by 2020 and state Medicaid programs strapped for cash, more scenarios like Arkansas are likely. The state of New York is presently reviewing the price of Orkambi and its impact on the state's Medicaid budget.

Patients Are Dying

In the United States, patients with insurance are being slammed with high out-of-pocket costs or being forced to stop working in order to qualify for government assistance and gain access to Kalydeco or Orkambi. Cystic fibrosis patients who have encountered sudden insurance changes have been sued for the cost of their drugs. Patients on Medicaid caught in onerous appeals processes in states like Arkansas have experienced sharp downturns in health. Parents of children with cystic fibrosis and adults with CF must spend hours on the phone each month gaining approval for unaffordable medicines.

Children abroad can't get access to treatment because the list prices are too high. These are children like:

- 14-year-old Joe Barnes and 19-year-old Oli Dillon in England, denied treatment because Vertex refuses to lower its prices.
- Valentina Maureira in Chile, who begged to die by euthanasia to end her suffering before cystic fibrosis killed her.
- Nine-year-old Australian boy Lucas Sorensen, who is getting sicker waiting for Orkambi.
- In Ireland, children and young adults died waiting for the Orkambi to gain approval in a years-long negotiation between Vertex and the government. Orkambi received funding for Irish adults and for children in April 2017 and for children in January 2018 in Ireland.

Conclusion

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.

Disclosures: I own 22 shares of stock in Vertex which I purchased in 2016 in order to be able to participate in shareholder meetings. P4AD is funded in part by the Laura and John Arnold Foundation which also provides funding to ICER.

To Whom It May Concern:

I am writing to share my experience as a mother of an 18-year-old son living with cystic fibrosis, Jack, and how Symdeko is improving his health, quality of life, and confidence in his future as he heads to college. I believe the report should be revised to include more information about how this medication is changing the lives of families and people living with the disease. Symdeko is the first medication added to Jack's daily care plan that targets the genetic defect causing cystic fibrosis. This medication does not simply help him manage his symptoms, it changes the game. It restores gene function alleviating the build-up of thick mucus that leads to lung infections and poor weight gain.

Jack was diagnosed with cystic fibrosis at birth due to meconium ileus. The first 18 hours of his life were a blur of activity. My husband and I went from the birthing center to the NICU, from radiology to surgery. And, of course, we endured the requisite torment of countless hours in waiting rooms not being able to be with our newborn son. We spent three weeks in the hospital with Jack feeling like we had failed each other and, worst of all, our little boy.

Finding our resilience, we forged ahead into a daily routine of feedings every 2-3 hours and chest physical therapy. A year into Jack's life, our physician told us that he needed to gain more weight if he was going to reach his growth potential. I remember leaving that appointment very disappointed. Weren't we doing enough? Were we giving him the right dose of enzymes? Months of work ensued for our family, addressing eating behaviors and adding feeding supplements to Jack's diet.

As he grew, we began to include inhaled medications (Pulmozyme and hypertonic saline), an airway clearance system (the Vest), and daily exercise to keep his lungs healthy. These therapies added two hours of treatments to our day as we held down full time jobs and Jack navigated school, sports, and club activities, not to mention quarterly clinic visits and days off due to pulmonary or GI flares. At the age of 12 Jack started seeing his providers independently, at 16 he took charge of refilling his medications, and now, as he prepares to leave for college, he has reached out to the adult cystic fibrosis center to introduce himself and set up a care system.

Jack is doing all that he can to maintain his health, but is seeing his lung function slowly decline. This year after treatment for two pulmonary exacerbations and MRSA, he and his team felt Symdeko would prevent further decline with little to no side effects. He has been taking it for a month. He is experiencing no side effects. He is maintaining his weight and has no pulmonary symptoms. He is hopeful this medication, in addition to his other preventative care, will allow him to enter college healthy and not miss any aspect of the experience. He will study political science and would like to practice law. As his mother, I want to see him pursue his dreams and live a full and rewarding life. Symdeko and any future medications that address the underlying genetic cause of cystic fibrosis will give him that chance.

I hope this letter will move you to consider revising the report to address how Symdeko and other similar medications are impacting the lives of people with cystic fibrosis today and adding tomorrows to their future.

Sincerely,

Kathryn A. Sabadosa

To Whom It May Concern:

I was diagnosed with Cystic Fibrosis at the age of 5. My brother had been very sick all of his seven years. After being misdiagnosed with chronic pneumonia for years, he was finally tested and confirmed for Cystic Fibrosis. I, too, was tested and was diagnosed with a "milder" case. While my brother was in and out of the hospital at least 4 times a year, my symptoms resided in my sinuses. I had my nasal polyps removed on a yearly basis but my lungs and digestion were okay. Unfortunately, in the 1970s and 1980s, we did not have the incredible medications that we have today to treat Cystic Fibrosis. My brother became sicker and sicker, spending his last years attached to oxygen outside of school and he passed away in the summer of 1988, a year before the CF gene was discovered. While I continued to fare well, despite even more polyp surgeries, my lung function began to decline into my 20s and my FEV lowered to 48.

I spend an hour in the morning and an hour at night doing my airway clearance treatments and three nebulizers. Every other month, I add an inhaled antibiotic, Cayston, to my regimen which is taken three times a day. I take about 25 pills a day and I am fortunate to be pancreatic sufficient so that does not include enzymes. I try to exercise at least 3 or 4 times a week but lately that has been difficult because I have been feeling sick for the past two months. I have taken 2 courses of steroids and am on my second oral antibiotic but I cannot seem to get rid of the infection I seem to have. I started having to spend two weeks in the hospital on IV antibiotics to fight infection, or "tune-ups," in my mid 20s and, depending on the year, would do home IV antibiotics every 18 months or so.

I began a strict regimen of physical therapy treatments twice a day with the Vest and visiting my clinic twice a week for manual and massage therapy to clear my lungs. By now, I was using nebulized treatments such as albuterol and pulmozyme, as well as Tobi but that made my chest tight. I started having to do "tune-ups" in my mid 20s and, depending on the year, would do home IV antibiotics every 18 months or so.

I was working full time in the music business and traveling a lot. Eventually, I wanted a career change and took a different job while I applied to school for Social Work. This job was extremely stressful and that took a toll on me physically. After 14 months, I had to go out on Disability to care for my health. I began working out, taking yoga, I did a cardio training at my CF clinic to help get me on an exercise regimen. My digestive problems went away after I stopped working and my lung function increased to 60. At this time, my doctor gave me the okay to get pregnant and I fulfilled my dream of becoming a mom. Twice. I feel so lucky that I had two successful pregnancies and felt great throughout. However, my lung function has once again dropped down into the 40s, 50s on a good day. At this point, I was hearing about the groundbreaking clinical trials that Vertex was conducting. Unfortunately, the trial, which turned out to be Kalydeco, was only for a small percentage of CF patients and I did not qualify. I also

did not qualify for the next drug coming down the horizon, which became Orkambi. The one that could possibly work for my mutations was another 5 years down the horizon. That caused me severe anxiety knowing that lung function decreases each year and there were no guarantees that this drug would work. I had also lost a few friends to the disease during this period so the thought of waiting so long depressed me. My doctor put me on anti-depressants for my anxiety as I felt like my anxiety was getting in the way of my parenting. I had become easily provoked and edgy, worrying if I would be around for my kids as they grew up.

Finally, my chance came to take part in a clinical trial for Ivacaftor/VX661. I had followed the stories of Kalydeco and Orkambi very closely and was waiting for that moment when I would suddenly take a deep breath and would feel a huge change. As I started the trial, I monitored every feeling in my body to see if I felt any different. Maybe, I did. I couldn't tell. I do know that at the end of the 8 week period, I got very sick. I had to do a month on IV antibiotics and postpone the next leg of the trial. After the second trial, I had the same problem and then was struck with the flu and went to the hospital for fluids. I was still optimistic. Maybe I had had placebo both times and when I rolled over to be on drug, I would feel the big jump in lung function.

I have now been on tezacaftor for about two years. I was worried about coverage now that it passed through the FDA but so far my insurance has approved it. We are about to switch insurances and I am crossing my fingers that the new one will also cover it. I am still waiting for the big jump and accept that I'm not getting it from this drug. I can't help but feel deflated that my lung function still holds in the 40s, between 42 and 50, depending on the day. I hear of people with two deltaF508s who just started the drug after its approval and they are relating great experiences. As with the patients who were helped a lot with Kalydeco and Orkambi, I am so happy for them but envious, as well, because I have been waiting for so long and this drug that was supposed to do great things for me, has not. However, I must look at the positive. I have not been very sick since I had the flu two years ago. I have not been on IVs since December of 2015/Jan 2016. My energy level until recently has been immense. I have been able to volunteer as an advocate for the Cystic Fibrosis Foundation, traveling to DC, Albany and Indiana. I was very active this past year in advocating for healthcare and protections provided by the Affordable Care Act. My friends joke that I probably do more than they, who do not have a lung disease. I have been able to raise my kids and be a big part of their lives, chaperoning them on field trips at school and participating in their activities. Some days, my kids likely even forgot for a little while that their mom has a terminal illness. My lung function has not increased but it has also not dropped. I am, however, once again, eagerly awaiting the next phase of CFTR correctors, the triple combinations. I remain optimistic that one of these will benefit me. I recently found out I am not eligible to participate in the clinical trial because of my mutation but will remain vigilant about jumping on as soon as I am possible.

I still spend an hour in the morning and an hour at night doing my airway clearance treatments and three nebulizers. Every other month, I add an inhaled antibiotic, Cayston, to my regimen which is taken three times a day. I take about 25 pills a day and I am fortunate to be pancreatic sufficient so that does not include enzymes. I try to exercise at least 3 or 4 times a week but lately that has been difficult because I have been feeling sick for the past month. I have taken 2 courses of steroids and am on my second oral antibiotic but I cannot seem to get rid of the infection I seem to have. I have a feeling I am going to break my streak and get a PICC line for IVs. For the first time that I can remember, I have been feeling out of breath and more congested than usual. I really am eager for these triples to show efficacy for my mutation. Anti-anxiety meds can only help so much.

I am still on disability, which is rather frustrating for me, but I cannot afford to have my health decline any more than it has so that when the new drugs that benefit me come out, I will be in the best physical shape that I can be in. It is my hope that there will be a one-time cure for Cystic Fibrosis in my lifetime. I plan to grow old with my husband and spoil my grandchildren. In the short term, I hope that there will be vast improvements on the groundbreaking drugs that are available now. I hope there will be CFTR and other drugs that will benefit 100% of the CF community and that my fellow CF patients will gain relief from this difficult disease. That also means that everyone, regardless of income, health status, job, or geographic location, will have access to adequate affordable healthcare so that they can have the opportunity to benefit from these incredible treatments.

Thank you for your time.

Sincerely,

Melissa Shiffman

April 12, 2018

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value"

Dear Dr. Pearson:

Patients Rising Now advocates for access to care, continuous innovation, and regulatory reforms that support patients living with chronic and life-threatening illnesses. Access to treatments spans affordability (patient out of pocket costs), insurance design, and physical access to treatment. Access to the right treatment at the right time is a matter of survival for many of these patients, and a requirement for them to live better and more productive lives.

We are committed to engaging patients, caregivers, physicians, the media, health policy experts, payers, providers and other health professionals to foster realistic, patient-centered, solution-oriented discussions so that those facing critical medical needs can amplify their collective voice to create lasting improvements for health care in the United States. That is, our goal is to advance a balanced dialogue and national conversation that tells the truth about health care in a just and equitable manner.

We appreciate the opportunity to provide our comments on ICER's March 15th draft evidence report, "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value."

Overall, we respect and encourage the trend toward value and will continue to lead meaningful conversations and a deeper dialogue around the meaning of value-related initiatives for patients. We believe patients' voices need to be a part of defining and assessing the value of their treatment plans along with the cost of all aspects of their care – including patient's direct out of pocket costs and patient's costs related to their ability to work, their need to travel for care, and other costs arising from either their medical conditions or care. As Mandelblatt et al., noted, "in frameworks to evaluate drug treatments, economic impacts would include drug costs, provider time and delivery costs, staff time, facilities and equipment overhead and costs, costs of treatment-related side effects and supportive care medications required, patient time and travel costs, and costs of all downstream events until death from the disease or other causes. To the extent that frameworks exclude portions of these costs, they result in biased recommendations."[i]

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…"[ii]), 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.[iii] ICER's approach is clearly contrary to the conclusions of leading health services researchers and economists who have stated that "No single perspective can represent the interests of all participants in value-based decisions."[iv] 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.

1. ICER's Process for Ultra Rare Conditions

We appreciate ICER developing modifications to its framework for ultra-rare diseases.[v] 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.

2. Patient Perspectives Concerning Draft Evidence Report on CF Therapies.

In ICER's draft evidence report about Cystic Fibrosis (CF) treatments, it is clear that the three new therapies described in ICER's draft evidence report are great advances for some patients with CF and their families. They each are examples of the progress of precision medicine and the science of genomics. However, they are also clearly not the end-goal for treating CF. Additional treatments that have better efficacy - or can be used for other mutations - are certainly needed, which is the main focus for patients with CF and their families.

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.[vi] 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 <u>will</u> become available in the future and that <u>may</u> 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, <u>not</u> the exception.

And concerning what Garrison et al.[vii] 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 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.

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.

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.

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 of the value of this intervention: _____."

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.[viii] 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.

3. 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."[ix]

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 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.

4. Budget Impact

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."

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 illusionary uniform U.S. health care system.

Conclusions & Recommendations

Patients Rising Now believes that ICER's work continues to inadequately reflect patients' perspectives about quality of life, functionality, the range of real patient's choices and goals, the spectrum of financial implications for new therapies, and practical options for increasing value for patients within the pluralistic U.S. health care system.

The only way value frameworks will ever be effectively used to benefit patients and society is when they consider input and perspectives from patients and their doctors based on the whole picture of the treatment journey because treating the whole patient is the most cost-effective means of treating the larger patient population. While there is much that can be done to streamline the use of our finite health care resources, sacrificing patient care to meet some arbitrary metric fails every professional and moral standard.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] Mandelblatt et al., "Evaluating Frameworks that Provide Value Measures for health Care Interventions," Value in Health, 2017 185-192

[ii] ICER Draft Evidence Report, "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value" March 15, 2018, page 5

[iii] https://icer-review.org/department/midwest-cepac-advisory-board/

[iv] Mandelblatt et al., "Evaluating Frameworks that Provide Value Measures for health Care Interventions," Value in Health, 2017 185-192

[v] "Modifications to the ICER value assessment framework for treatments for ultra-rare diseases" November 2017 https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf

[vi] Garrison et al., "Toward a Broader Concept of Value: Identifying and Defining Elements for an Expanded Cost-Effectiveness Analysis," Value in Health (20) 2017, 213-216.

[vii] Ibid.

[viii] https://icer-review.org/department/midwest-cepac-members/

[ix] Letter from Preston W. Campbell, III, MD, President and Chief Executive Officer CFF Foundation Letter to ICER on November 20, 2017

Comments regarding the Cystic Fibrosis: Draft Evidence Report

1. The background is improved. I suggest you remove the reference to *Strep pneumoniae* 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.
2. 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.
3. Management (page 10): I suggest you change CPT to airways clearance or acknowledge there are devices that are used as well.
4. 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)
5. 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.
6. Outcomes (page 14): why is transplantation not included?
7. Insights gained (page 18): I think you have this section right.
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.
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.
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.
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.
12. NICE guidelines (page 23): This should be noted to be UK specific. There are also ECFS guidelines on antibiotics and standards of care.
13. Ivacaftor data (page 35): Using exacerbations as a clinical endpoint requires a longer duration than was used 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"?
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.
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?
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.
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.
19. The very next paragraph left me perplexed; what does that opening sentence even mean? This paragraph should be deleted.
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.
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 *Pseudomonas* in cultures. One additional observation for CFTR modulators is the impact on microbiology with a lesser proportion growing *Pseudomonas*. 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.

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.
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.
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%.
25. 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.
26. 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.

Submitted by:
Patrick A. Flume, M.D.
Professor of Medicine and Pediatrics
The Powers-Huggins Endowed Chair for Cystic Fibrosis
Director, Medical University of South Carolina Cystic Fibrosis Center

To Whom It May Concern,

I'm writing to share the enormous positive impact that the CFTR modulator drug Ivacaftor has had on my child. My son Brady was diagnosed with cystic fibrosis at birth in 2007, and struggled with many of the classic symptoms of cystic fibrosis. Brady spent several hours every day of his young life treating the symptoms of his disease. We battled the thick mucus in his airways with inhaled breathing treatments and airway clearance treatments 2-4x/day. Brady also suffered from serious upper respiratory inflammation that completely robbed him of his sense of smell. By the time he was 4 years old, he had already had two surgeries to remove polyps from the sinuses that were unable to be controlled with steroids. The combination of thick mucus and inflammation led to frequent lung and sinus infections, requiring treatment with heavy duty antibiotics.

Brady also suffered from pancreatic insufficiency, leading to difficulty with digestion and proper growth. Abnormally thick mucus in his gut also negatively impacted his ability to absorb nutrition. Digestive enzymes have been required with every meal he has ever eaten since he was an infant.

On February 10, 2012, Brady took his first dose of Ivacaftor. Within days, my husband and I noticed that his energy had increased significantly, and his breathing had changed dramatically. The inflammation in his sinuses began to disappear, and his sense of smell was regained within days of starting the drug. Brady spent weeks exploring the smells he had been missing in the world around him after Ivacaftor came into his life. His appetite also experienced a significant bump with his newfound sense of smell.

With his bedroom right across the hall, my husband and I had become accustomed to hearing Brady snore and struggle to breathe all night, every night. Within just a few days of starting Ivacaftor, his breathing became quiet and effortless. The thick sticky mucus that used to clog his lungs and cause him to cough until he vomited changed to the thin watery lubricant needed for proper organ function.

Although Brady is still pancreatic insufficient, Ivacaftor also had a huge positive impact on his digestion and growth. The thick CF mucus in the digestive tract was normalized, allowing for better nutrient absorption and less stomach pain.

Brady was fortunate enough to begin treatment with Ivacaftor at only 4 years old—before he had sustained serious permanent damage to his lungs. Because Ivacaftor is tailor made to treat the root dysfunction of the CFTR protein, Ivacaftor appears to have halted the progression of lung disease in Brady's body. Today, as a 10 year old, his lung CT scan looks completely normal, which wouldn't be possible without Ivacaftor. Unlike most children with CF, Brady has no baseline cough, and excellent lung function because of Ivacaftor.

Prior to Ivacaftor, cystic fibrosis demanded center stage in our lives every single day. It felt like we were constantly battling the symptoms, but always remained two steps behind. The smallest virus could mean a serious lung exacerbation, and hours of extra treatment time. Since beginning Ivacaftor, Brady seems much more resilient at weathering routine viruses with minimal intervention. He is also more tolerant to changes in air quality, allowing us to enjoy more time outside. As a family, we feel free to live normal lives—without the constant fear of exposure to common pathogens.

My husband and I were thrilled to learn that lab data supported the phenomenon we were witnessing with our own eyes. Prior to Ivacaftor, Brady's sweat test result was 105 mmol/L—a typical number for classic cystic fibrosis. After treatment with Ivacaftor, his sweat test numbers plummeted to 17 mmol/L, indicating a marked increase in CFTR protein function in his body. The taste of salt on my lips when I kissed Brady's skin, disappeared.

Ivacaftor has been nothing short of a miracle for our son. Not only has Ivacaftor added immeasurable quality to Brady's life, it is also expected to add decades to his life expectancy. As parents, we are now able to hope for a bright future for our child. Because of Ivacaftor, my husband and I experience much less anxiety related to the disease. It is difficult to comprehend the weight of the burden of cystic fibrosis, until that burden has been lifted. We live with an abundance of gratitude for Ivacaftor, and greatly appreciate the "normal" days we have together as a family.

Thank you for the opportunity to share the details of our experience with Ivacaftor. We celebrate the anniversary of Brady's first dose every year on February 10th, and will always consider the drug a dream come true for our entire family.

Sincerely,

Rebecca Schroeder

Mother of Brady Schroeder, age 10 (G551D, DF508)

Personal comments by Scott Grosse, health economist, on the economic inputs section of "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value" Draft Evidence Report, ICER, March 15, 2018

1. 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 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.

2. The assumed annual drug cost of ivacaftor is $309,841.58. That is a reasonable approximation of the gross 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.

3. 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 *Value in Health* (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.

4. 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.

5. 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 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.

6. 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.

7. 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.

8. 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).

9. 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 *Health Services Research* 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.

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April 12, 2018

BY ELECTRONIC DELIVERY

Steven D. Pearson, M.D., M.Sc., FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Response to ICER draft evidence report by Vertex Pharmaceuticals concerning ivacaftor (KALYDECO®), lumacaftor/ivacaftor (ORKAMBI®), and tezacaftor/ivacaftor (SYMDEKO™)

Dr. Pearson:

This letter serves as Vertex's response to ICER's draft evidence report related to its review of Cystic Fibrosis Transmembrane Conductance Regulator Modulators (CFTRm), specifically Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor), discovered and developed by Vertex Pharmaceuticals Incorporated (Vertex).

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),[1,2,3] and have been shown to have significant clinical benefits for the patients who are eligible for Vertex's currently marketed cystic fibrosis (CF) therapies.[4,5,6,7,8] 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.[5,6] 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.[9] CFTRm offer major improvements in quality of life and/or length of life for many patients with CF[4,10] 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.

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"[11] and the discouragement of innovative science.

Below, we outline several concerns we have after reviewing the draft evidence report.

* * *

We continue to assert that traditional cost per QALY frameworks are not appropriate for evaluating innovative medicines for rare diseases, and especially for lifelong therapies used to treat chronic illnesses. This is underscored by several outcomes presented in the evidence report that show how non-evidence driven and arbitrary choices in model design and estimation result in incremental cost-effectiveness ratios, and thus value-based prices, that do not reflect the true value of CFTRm:

1. 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 $ppFEV_1$ 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.

2. 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[12]. 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 $ppFEV_1$, ICER asserts that many aspects of the societal perspective, including caregiver costs, not intrinsically tied to $ppFEV_1$ could not be captured. This highlights the limitations of this model in capturing the full benefits of these innovative medicines.

3. 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)."[13] 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.

4. 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.[14,15,16] 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-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.[17] Inclusion of this LOE assumption is consistent with all published models examining

CFTRm cost-effectiveness.[14,15,16] 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.

* * *

Vertex has committed more than twenty years to the development of medicines that treat the underlying cause of CF. Since 2012, we have brought to market three medicines that do exactly that, directly improve the lives of CF patients and their families. We stand by the value of our medicines and the long-term benefits that they bring to people with CF. We sincerely hope that ICER takes the above comments into consideration, and we welcome the opportunity to address any questions you may have about the information detailed above.

Sincerely,

Jaime Rubin Cahill, MA, MPH
Executive Director, Health Economics and Outcomes Research
Vertex Pharmaceuticals

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To Whom It May Concern,

My name is Bill Elder, Jr and I was diagnosed with Cystic Fibrosis when I was 8 years old. My genotype is delF508/G551D. From childhood up until starting ivacaftor I had numerous CF exacerbations nearly always requiring antibiotics and often hospitalization. To reduce the frequency of these exacerbations I would have to do hours of therapy a day with the Vest and nebulized Pulmozyme, hypertonic saline, and antibiotics. In addition to the chest physiotherapy and nebulized treatments I take numerous pills everyday including digestive enzymes, antibiotics, vitamins, and now ivacaftor.

When I was first diagnosed with Cystic Fibrosis the life expectancy was in the late 20s and even with rigorous adherence to my therapy regimen I was unsure if I would be able to live past early adulthood. It was the optimism of my physicians and the light on the horizon of the drug pipeline that set me on the path to become a doctor against that grave prediction of my mortality. My hope was rewarded countless times throughout my life with the advent of each new medication and another year added on to the life expectancy. Even still, the specter of an early death was just postponed with every new treatment. In college I quickly realized my calling in life was to become a physician, but at this point my lungs were colonized with Pseudomonas and my lung function was starting to decrease with every exacerbation. I still vividly recall the sunny day at Stanford when I received a call from my CF doctor and mentor, Dr. Accurso, telling me that there was a new drug about to enter Phase II trials that could correct the basic defect and potentially change what it means to have Cystic Fibrosis. I took a chance on my dreams and in the months before I started medical school at Wright State University ivacaftor was approved. With my first dose I regained my sense of smell which had been diminished from nasal polyps and thick secretions. With the doses that followed I stayed healthy enough to become a doctor. I was able to decrease the time spent doing therapy each day, no longer had exacerbations, and my FEV1 became rock-solid in the high 90s. I went from working tirelessly to keep myself healthy to working tirelessly to keep my patients healthy.

The value of CFTR modulators cannot be adequately measured in lung function, life expectancy, or even quality of life. For me the most important effect of ivacaftor is not on the quality or duration, but on the meaning of my life. One pill twice a day has enabled me to answer the call to public service as a resident family physician working in an federally qualified health center.

Please consider the value that one devoted family physician adds to their patients, their community, and the nation as a whole when considering medications like ivacaftor.

Sincerely,
William Elder, Jr, MD