cfri Cystic Fibrosis Research Inc.

Voice of the Cystic Fibrosis Patient

A Summary Report of the Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis

Hosted by Cystic Fibrosis Research, Inc. (CFRI) — Held October 29, 2018

Thank you to our partners in the Cystic Fibrosis Engagement Network

for their Participation and Support of the Externally-Led Patient-Focused Drug Development Meeting.

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Voice of the Cystic Fibrosis Patient

A report resulting from an Externally-Led Patient-Focused Drug Development Meeting Corresponding to FDA's Patient-Focused Drug Development Initiative

Externally-Led Public Meeting Date: October 29, 2018

Hosted by

CFRI

Cystic Fibrosis Research, Inc.

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Point of Contact/Corresponding Author:

Siri Vaeth, MSW
Executive Director
CFRI
Email: svaeth@cfri.org

Additional input to this report was provided by Richard B. Moss, MD, and James Valentine, JD, as well as by CFRI Staff Members Sabine Brants, MA, Jacob Fraker and Rachel Wycliffe.

Dear Friends,

Cystic Fibrosis Research, Inc. (CFRI) is honored to share *Voice of the Cystic Fibrosis Patient*, a summary report of the experiences, preferences, hopes, and fears shared by those attending CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis held October 29, 2018. On this momentous day, the diverse and complex patient experience with cystic fibrosis (CF) was shared with representatives of the Food & Drug Administration (FDA), healthcare providers, researchers, biotechnology company representatives, and fellow members of the CF community, so as to expand understanding of disease impacts, the critical need for new therapies, and our community's willingness to actively participate in clinical trials and to assume risks so as to advance drug development.

When CFRI was founded in 1975, children diagnosed with CF were unlikely to survive childhood. While we celebrate the development and approval of novel CF therapies and the related increase in life expectancy, we still have work to do. The daily burden of CF care is massive and the emotional and physical toll significant. Many individuals with CF cannot benefit from recently approved therapies, and a cure remains elusive.

We are very grateful to the individuals with CF and the parents of those with CF who participated as panelists, as well as to Dr. Ahmet Uluer, Director of the adult program at the combined Boston Children's Hospital and Brigham & Women's Hospital Cystic Fibrosis Center, for providing an overview of the disease. We thank the many representatives of the FDA who attended either in person or remotely, and recognize both Dr. Robert Lim, FDA Center for Drug Evaluation and Research, and Dr. Tejashri Purohit-Sheth, FDA Center for Biologics Evaluation and Research, for sharing their time and insights.

CFRI was able to offer this vital meeting due to the generous support of our sponsors, listed in this report, all of whom are actively involved in the development of cystic fibrosis therapies. We are grateful to the other CF-related organizations that helped CFRI bring the meeting to fruition and engage our national patient community. These include our fellow members of the Cystic Fibrosis Engagement Network: Boomer Esiason Foundation, Emily's Entourage, Rock CF Foundation, CF Lifestyle Foundation and the Bonnell Foundation, as well as Attain Health, Cure CF, and the Cystic Fibrosis Foundation.

Event planning was a complex undertaking in light of cross-infection risks that prevented members of our community from being together in the same room. There was bitter irony in convening a meeting to share the CF patient voice that could not be jointly attended by those living with the disease. Beyond the minor logistical challenge, far more devastating is the lifelong isolation from one's CF peers that is the result of cross-infection concerns. The impacts of cystic fibrosis extend far beyond the physical.

Our needs as a CF patient community and our measurement of therapeutic impact may be unique. While the experiences shared within this report represent only a fraction of the 30,000 individuals in the United States living with this rare disease, they are compelling and consistent in their urgent call for new therapies.

Collectively and individually, our voices matter.

Thank you,

Bill Hult
President, CFRI Board of Directors

Siri Vaeth, MSW
Executive Director, CFRI / Mother of an Adult Daughter with CF

CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis Voice of the Patient Report

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Report Summary

Cystic fibrosis (CF) is a multi-systemic and debilitating genetic disease impacting 30,000 people in the United States. Primarily known for causing progressive lung disease, CF leaves no organ system unscathed. Current FDA-approved therapies are not a cure, and present a significant burden of care for patients and their caregivers. While life expectancy for those with cystic fibrosis has expanded, it remains a fatal disease, and half of those who died last year were under the age of 30. It was with a sense of urgency that members of the CF community joined together at CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis in Hyattsville, Maryland on October 29, 2018, to share with Food and Drug Administration (FDA) representatives their experiences living with this complex disease, their perspectives on CF therapies, clinical trials and drug development, and their fervent hope that both drug developers and FDA regulators will intensify their efforts to advance more effective therapies for cystic fibrosis.

The meeting was part of FDA's Patient-Focused Drug Development Initiative, which seeks the patient perspective to provide context as regulatory decisions are made for new therapies, both during the drug development process and during the review of marketing applications for new drugs. CFRI's partners in the Cystic Fibrosis Engagement Network, including the Boomer Esiason Foundation, Emily's Entourage, Rock CF Foundation, Bonnell Foundation, and CF Lifestyle Foundation, helped to promote the event to their constituents, as did Attain Health, Cure CF, and the Cystic Fibrosis Foundation. Approximately 50 people attended the meeting in person, while an additional 364 people watched and participated online via CFRI's webcast. Those in attendance included individuals with cystic fibrosis, family members of those with CF, FDA representatives, CF researchers and clinicians, and representatives of pharmaceutical and biotechnology companies.

The meeting goals and objectives for the meeting were as follows:

- To enhance understanding of the patient perspective on the complex impacts and burden of disease, adherence issues, and improvements that may be gained through potential treatments.
- To enhance understanding of the individual with CF's perspective on life with the newest therapies aimed at halting the progression of the disease.
- To expand and increase the breadth of people with CF engaged in defining benefit-risk considerations from the perspectives of people with CF across the varying degrees of the CF health spectrum, as this has not been formally explored for CF.
- To contribute meaningfully to the advancement of the development of treatments for CF through collaborative, systematic engagement of people with CF and their caregivers.
- To explore and enhance opportunities between individuals with CF and biopharmaceutical companies regarding input from the perspective of people with CF on conducting clinical trials.
- To enhance understanding on the unique needs and available therapeutic options for post-lung transplant individuals with CF.

The day was divided into morning and afternoon sessions, and facilitated by James Valentine, JD, MHS. The morning's topic was "Disease Symptoms, Challenges and Impact on Quality of Life," while the afternoon topic explored "Perspectives on Current Approaches to Treating CF; Goals for Potential Treatments; Drug Development Issues/ Clinical Trials."

Two panels – one comprised of parents of children with cystic fibrosis and another comprised of adults living with the disease – launched the group discussions during the morning and afternoon sessions. Panelists participated from across the United States, including California, Montana, Pennsylvania, Michigan, Kentucky, Tennessee, New York, and Delaware. CFRI's executive director provided opening remarks, after which NFL star and CBS football commentator Boomer Esiason, whose son Gunnar has CF, welcomed meeting attendees in a recorded statement. Prior to hearing from individuals living with cystic fibrosis, Dr. Ahmet Uluer, Director of the adult program at the combined Boston Children's Hospital and Brigham & Women's Hospital Cystic Fibrosis Center, provided an overview of the disease.

Individuals with CF often harbor harmful pathogens in their lungs, and due to the risk of cross infection between adults with CF, several panelists called in to make their statements and join in the discussion. In order to expand participation to the national cystic fibrosis community, as well as to address these cross-infection risks, the meeting was live streamed, and during group discussion periods, remote attendees could call in and email their comments. The recording of the meeting was posted on CFRI's YouTube channel, where an additional 392 people have viewed it. The full recording can be seen here: https://tinyurl.com/y77jt99h. Viewers were provided a link to answer polling questions identical to those asked during the day of the meeting. The resulting information provided by 61 additional respondents has been incorporated into the report.

Through the presentations by invited panelists, comments provided by attendees in person and by phone, polling results, and emailed comments from remote attendees, a tremendous amount of information and brutally honest perspectives on life with cystic fibrosis were generated. Cystic fibrosis triggers multi-faceted impacts. By necessity, this report reflects the input of those living with the disease who participated in this event; it is likely that there are symptoms, impacts on daily life, and burdens of care experienced by members of the CF community that are not reflected in this summary report. Key themes from the meeting are summarized below:

Cystic fibrosis has a devastating impact upon the lives of those living with the disease.

- Cystic fibrosis (CF) is a complex, capricious, multi-systemic, and debilitating disease. The autosomal recessive genetic disorder is caused by mutations in a gene on the seventh chromosome that makes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Only 30,000 people in the United States have been diagnosed with cystic fibrosis.
- Respiratory complications were the primary challenge and source of concern for meeting participants, including lung infections, lung bleeds and lung collapse, yet it was consistently stressed that mental health issues and gastrointestinal complications also significantly impact CF patients' quality of life. Other common symptoms include CF-related diabetes, sinus polyps, liver disease, osteoporosis, and reproductive health challenges.
- Cystic fibrosis negatively impacts people's ability to spend time with friends and participate in social activities, as well as their attendance at work and/or school. Those living with CF worry deeply about advancing lung disease and death, and well as their ability to maintain financial stability and live independently.

Cystic fibrosis is a highly variable and heterogeneous disease, resulting in diagnosis, treatment and clinical trial design challenges.

- There are approximately 2,000 mutations of the CFTR gene that cause cystic fibrosis, with varying disease expression. For those with rare mutations, diagnosis may be challenging. Even when patients have the same mutation, their disease symptoms and response to therapies can vary widely.
- Therapies for cystic fibrosis create a significant daily burden of care, with patients spending between 2 and 5 hours per day following their medical regimen, with hopes only of slowing disease progression. Therapies include airway clearance, multiple nebulized medications (bronchodilators, hypertonic saline, DNase, antibiotics), pancreatic enzyme replacement, insulin, oral antibiotics, vitamins, IV antibiotics, enteral feedings, and mental health interventions. New CFTR modulator drugs have helped improve lung function for some, but they are not a cure, and are not effective for all CFTR mutations.
- Side effects of medications often worsened health. Many of the drugs can damage the liver; some IV antibiotics lead to permanent deafness or trigger dangerous allergic responses; post-transplant immunosuppressants increase the risk of cancer and are nephrotoxic; steroids used to reduce inflammation exacerbate CF-related diabetes; increasingly pathogens develop resistance to available antibiotics.
- Individuals with CF who have received double lung transplants still must cope with the impacts of cystic fibrosis, along with an often debilitating regimen of immunosuppressants to hold off organ rejection.

- Clinical trials may be challenging due to the multiple mutations found among the CF population. Clinical trial exclusions that include lung function measures, age, specific mutations, BMI, and/or pathogens in the lungs may significantly limit the number of eligible patients for participation.
- Cystic fibrosis remains a progressive disease, and the vast majority of respondents noted that their symptoms had worsened over time.

Individuals with cystic fibrosis desire more effective treatments with reduced side effects and burden of care, and are committed to participation in the drug development process.

- The CF community has a strong desire for new therapies that reduced lung infections which lead to permanent lung function loss, pneumothorax, hemoptysis, hospitalizations, IV antibiotics, and lost work/school time. Individuals seek therapies that improve their ability to breathe. New drugs to address gastrointestinal complications must be developed. In light of the current treatment burden, new therapies that do not require additional time would be highly valued.
- The cystic fibrosis community is known for its enthusiastic participation in clinical trials, and this perception was confirmed by meeting attendees, the majority of whom were clinical trial participants – either currently or in the past.
- Meeting participants expressed strong willingness to assume risks in participation with clinical trials, also indicating that distance, placebo, blood draws, missed work, and multiple clinic visits would not discourage their participation.
- The desire for enhanced research, drug development and trials for members of the CF community with nonsense and other rare mutations was passionately expressed.
- A common sentiment expressed at the meeting was the desire to participate in clinical trials not only for one's own personal health, but with the hope that others might benefit in the future.
- Individuals with cystic fibrosis have a strong desire to participate in trials, and are often frustrated when they are excluded due to their FEV1. A consistent theme was a desire for drug developers and the FDA to consider expansion of criteria for CF clinical trials beyond the current FEV1 to include number of exacerbations, quality of life, weight, etc.
- N-of-1 studies were encouraged due to the number of rare mutations in the CF community.

The Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis was a powerful event in illuminating the voice of those impacted by cystic fibrosis. It is hoped that this markes the beginning of an ongoing conversation between FDA and the cystic fibrosis patient community so as to inform those who assess the value and efficacy of CF-related therapies. Many CF mutations are not responsive to CFTR modulating drugs, and for those with cystic fibrosis, every day without new therapies matters. The burden of care is massive. The cataclysmic fall to transplant or death is far too common. In light of this, the cystic fibrosis community is unfailing in its commitment to assume risks and participate in clinical trials so as to advance drug development.

Introduction

CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis was held on October 29, 2018, in Hyattsville, Maryland. At this meeting, individuals with cystic fibrosis and their loved ones had the opportunity to share their experiences living with the disease, and their perspectives on cystic fibrosis (CF) therapies, including those currently in use and those in development. Through panel presentations, facilitated discussions, and input from the nationwide CF community via phone and email, those in attendance heard of the diverse, serious health complications and significant burden of care experienced by those with cystic fibrosis, as well as preferences hopes for future therapies.

While the meeting was not hosted nor organized by the United States Food and Drug Administration (FDA), a liaison from the FDA's Center for Drug Evaluation and Review provided CFRI with planning recommendations and promoted the meeting to FDA officials and staff. The Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis was attended by individuals with cystic fibrosis, family members of those with CF, FDA officials, CF researchers, CF clinicians, and representatives of pharmaceutical and biotechnology companies.

This report provides a summary of the experiences and perspectives shared by individuals with cystic fibrosis and their families during the meeting, as well as in the weeks immediately following. The recording of the day's meeting was publicly posted, and polling information and individual input was solicited from members of the CF community unable to attend the day of the event. Cystic fibrosis is a complex disease with multi-faceted impacts. By necessity, this report reflects the input of those living with the disease who participated in this event; it is likely that there are symptoms, impacts on daily life, and burdens of care experienced by members of the CF community that are not reflected in this summary report.

Overview of Cystic Fibrosis and Available Treatments

Cystic fibrosis (CF) is a complex, multi-systemic and debilitating autosomal recessive genetic disorder, caused by mutations in a gene on the seventh chromosome that makes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Only 30,000 people in the United States have been diagnosed with cystic fibrosis. One must have two copies of the mutated gene to have the disease.

The cystic fibrosis transmembrane conductance regulator (CFTR) gene provides the body instructions on the formation of a complex pore or channel protein across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. When functioning properly, the CFTR channel transports negatively charged particles, keeping the mucus that lines the airways and other organs in a fluid state with the proper balance of salt and water. It also regulates the function of many other cell processes, for example the absorption of sodium and liquid from the airways and aspects of host defense against infection. For those without CF, mucus is watery, protecting the linings of organs and moving bacteria out of the body. With cystic fibrosis, the genetic mutation interferes with this process– leading to a thick sticky mucus that easily becomes infected, clogging the airways, ducts and passageways of the respiratory, digestive, endocrine, and reproductive systems--and causes inflammation, infection, and progressive organ damage.

Approximately 2,000 mutations of the CFTR gene have been discovered, though of the most common mutations, only five occur at a frequency more than 1%, and less than 20 mutations occur at a frequency greater than 0.1%. (Cystic Fibrosis Mutation Database). CFTR mutations have been grouped into six classes, determined by the manner in which the mutations impact the CFTR protein structure and function. Because mutations within the same class may still cause diverse symptoms and respond differently to therapies in different people, and conversely a single mutation can produce dysfunction in more than one class, it is predicted that mutations will soon also be classified by "theratype," to indicate what therapy the mutations respond to in laboratory-based functional tests.

The symptoms of cystic fibrosis can vary widely from person to person, based on factors such as genetic mutation, impact of other genes and their products, age of diagnosis, environmental exposures, and other health issues. While primarily known as a progressive lung disease, frequent symptoms of CF include salty tasting skin, persistent cough, frequent lung infections (exacerbations), sinus infections, nasal polyps, poor growth and difficulty gaining weight,

frequent bowel movements with greasy or bulky stools, wheezing, shortness of breath, meconium ileus, rapid dehydration, and intestinal blockages. Men with CF usually have an absence of the vas deferens, leading to infertility.

Cystic fibrosis-related diabetes (CFRD) is a common complication of cystic fibrosis due to scarring of the pancreas and dysfunction of glucose-regulating cells. It is estimated that one out of five teenagers will be diagnosed with CFRD, and approximately 40% of adults will be diagnosed. There is a strong correlation between uncontrolled blood sugar levels and weight loss, worsening lung function, and an increased risk of death (Lewis et al, 2015).

With advancing lung disease, bronchiectasis (ballooning and dysfunction of airways) and pneumothorax (collapse of the lung) are common complications. Hemoptysis, in which inflamed blood vessels adjacent to airways rupture and bleed into the lungs, is not uncommon among adults with CF, and can be life- threatening. Some individuals with CF experience liver disease and gallstones when the hepatic and biliary ducts that carry bile from the liver and gallbladder to the small intestine become blocked and inflamed.

Bone disease impacts many individuals with CF. CFTR is expressed in certain bone cells, and when compounded with gastrointestinal issues that impede Vitamin D absorption, and the fact that steroids are frequently prescribed to CF patients, weakened bones (osteopenia and osteoporosis) often result.

While new therapies have increased the life expectancy for those with cystic fibrosis, there is still no cure. CF is a capricious disease, and it is difficult to predict its course. For those born in recent years who are able to utilize new therapies prior to the onset of severe symptoms, the predicted age of survival is approximately 47 years. Of abiding concern however, is the median age of death, which still remains around 30 years (2017 Cystic Fibrosis Foundation Patient Registry).

The thick sticky mucus in the lungs of those with cystic fibrosis provides an optimal environment for opportunistic microbial pathogens to thrive. Patients with CF are likely to culture (and often be colonized with) hardy bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *nontuberculous Mycobacteria*, and/or other bacteria. Those with CF are also prone to certain fungal infections such as *Aspergillus fumigatus* and respiratory viral infections. The risk of passing these pathogens between persons with CF is considered to be very high, and as such, most cystic fibrosis clinics and CF-related organizations have strict infection control protocols in place, and it is recommended that those with CF not come in close contact with each other. While these recommendations may reduce physical risk, they have also contributed to symptoms of depression and anxiety among individuals with CF, who often feel increasingly isolated due to their disease.

Mental health issues are increasingly recognized in the cystic fibrosis community. Higher rates of depression and anxiety have been found in individuals with CF compared to the general population. The International Depression Epidemiological Study (TIDES) examined this issue in over 6,000 persons with CF and over 4,000 caregivers of children with CF (from birth to age 18). Depression and anxiety symptoms were 2 to 3 times higher than the general population, (Quittner, 2014). Higher rates of depression have been correlated with health indicators of worse respiratory function and lower body mass index (BMI [Snell, 2014]).

Almost all men with CF are infertile due to congenital absence of the vas deferens. Those wishing to father a child with their partner must consider options including assisted reproductive therapies. Women with CF are able to conceive, though often this is difficult due to the thicker cervical mucus that can interfere with fertilization, or due to the irregular menstrual cycles experienced by women with low body weight. For many women wishing to have children, surrogacy or adoption is the only option due to health complications, or for women post-transplant, due to the medications required to prevent organ rejection.

While cystic fibrosis is found in every race and ethnic group, the prevalence varies widely, with the majority of those diagnosed of Northern European ancestry. According to the National Institutes of Health, in the United States, the disease occurs in 1 in 2,500 to 3,500 Caucasian newborns, 1 in 17,000 African Americans and 1 in 31,000 Asian Americans. The Cystic Fibrosis Foundation's Patient Registry for 2017 shows that nearly 9% of patients identify as Hispanic. Mutation prevalence varies among racial and ethnic groups, with associated disease severity. For example, in

California, despite controlling for age of diagnosis and access to healthcare, Hispanic children with CF have earlier onset of severe disease symptoms and are three times more likely to die earlier than their non-Hispanic CF peers.

Every state in the U.S. now includes cystic fibrosis in a newborn screening panel. The screening processes differ between states. For many families, this is the first identified case of CF in the family. Approximately 1 out of 6 babies with CF will be born symptomatically with meconium ileus, a blockage of the intestine that may require immediate surgery. Depending on the state, newborn testing may only screen for some of the most common mutations that cause CF. As such, there are cases that are identified later when symptoms indicate undiagnosed health issues. In these cases, as well as to confirm screening results, doctors recommend a sweat test, to measure the amount of salt in a person's perspiration, or a more detailed genetic test, in which a blood sample or cells from the inside of the cheek are analyzed for a broader range of mutations.

Until very recently, therapies to treat cystic fibrosis were solely focused on minimizing symptoms of the disease. New CFTR modulator therapies – which are mutation specific – have provided some individuals with a drug to address the underlying cause of the disease. Initially approved by the FDA in 2012 for people with CF with the G551D mutation, ivacaftor (Kalydeco®) was the first CFTR modulator drug which successfully assists the "gates" of the CFTR protein to stay open so as to allow more chloride ions to move into and out of the cells and improve the balance of salt and water. Referred to as a "potentiator," Kalydeco®, taken as a pill, is now an option for CF patients over one year of age with one of 38 CFTR mutations, covering approximately 10% of the CF population. By 2015, a two-drug therapy with ivacaftor and lumacaftor (the latter referred to as a CFTR "corrector" because it improves delivery of CFTR molecules to the cell membrane; the combination is marketed as Orkambi®) became available to those with two copies of the F508del mutation – the most common genetic basis of CF, found in nearly half of all patients, and now available from two years of age. And in 2018, a new two-drug combination of the CFTR corrector tezacaftor and ivacaftor (Symdeko®) became available to those at least 12 years old with two copies of the Fdel508 mutation, and also for those with one F508del and one of 26 other drug-responsive CFTR mutations. Currently several promising triple drug combinations are being studied to improve drug coverage to approximately 90% of CF patients.

It is crucial to remember that CFTR modulator drug therapies are not a cure, however, and their use is limited to those with specific mutations. There are many other CF patients who have no CFTR-modulator options, and even those who are able to benefit from these new drugs must still follow a complex and time consuming medical regimen that usually requires anywhere between 2 and 5 hours per day. This regimen often includes a series of inhaled nebulized medications: bronchodilators to open the airways, dornase alfa to thin mucus, and inhaled antibiotics (tobramycin, colistin, and aztreonam) to fight infections. Patients must also use equipment (mechanical vests, Aerobika, Acapella, etc.) and exercises to dislodge and clear mucus from the lungs. The lung infections that are prevalent among those with CF may require oral, inhaled and IV antibiotics. Due to frequent lung infections requiring IVs, many individuals with CF have a catheter port placed surgically, and hospitalizations to treat lung exacerbations may be frequent.

The use of antibiotics is common to treat the pathogens found in the airways of those with cystic fibrosis. There is an ongoing need to develop new classes of antibiotics, as some strains of bacteria are increasingly resistant. The side effects from these antibiotics can be debilitating, including allergy, nausea and fatigue. Certain IV antibiotics – most commonly tobramycin – can cause ototoxicity and permanent hearing loss.

The thick mucus caused by CF can also block ducts in the digestive system – including in the pancreas – causing severe nutritional and digestive problems. Enzyme replacement capsules are usually necessary before every meal to digest food properly. Due to absorption issues, supplemental vitamins and a diet that maximizes healthy weight gain must be adhered to. Low BMI is associated with lung function decline, and those who cannot maintain their weight may need to have a feeding tube placed for supplemental feedings to boost calorie intake. For those who experience distal Intestinal obstructive syndrome (DIOS), a blockage of the intestines, polyethylene glycol-electrolyte solutions may be enough; if a complete blockage occurs, patients may need to be hospitalized to have a nasogastric tube placed or even require surgery.

Sinus disease is treated with regular nasal saline irrigations and medications such as antihistamines, corticosteroids and antibiotics. Individuals with CF often develop nasal polyps that must be removed surgically.

Cystic fibrosis–related diabetes (CFRD) can be very difficult to manage. It is different from Type I and Type II diabetes that occur in people without CF, and must be closely monitored via glucose testing. It is most often treated with insulin. Many individuals with CF utilize continuous glucose monitors and insulin pumps.

For many individuals whose lung disease has advanced significantly, a double lung transplant is the only life-prolonging option. Lung transplantation is a complex surgery, which is physically and emotionally challenging. Many factors are considered when one is evaluated for lung transplantation, including the patient's physical and emotional health, quality of life, psychosocial support, financial capacity, and commitment to the rigorous post-transplant medical regimen. According to the Cystic Fibrosis Patient Registry, 250 individuals with CF had a lung transplant in 2017. Nearly 10% of those receiving lung transplants were under the age of 18. Transplantation is fraught with risk, and organ rejection, chronic lung allograft dysfunction (CLAD), infections, cancer, kidney disease, and other complications are common. A complex medical regimen must be adhered to Post-transplant. Those who have had a transplant still have cystic fibrosis in the rest of their body, and the health care regimen and complications associated with CF also continue.

Cystic fibrosis is thus an extremely multi-faceted, complex and variable disease that impacts nearly every organ system. There are multiple symptoms and complications, both physical and psychosocial. The treatment regimen is complex and burdensome, requiring hours each day with no respite. Due to cross infection risks, those with CF experience social isolation and associated depression and anxiety. While new therapies have improved life expectancy, the median age of death is only 30, and there is no cure. Due to the complex nature of the disease, the significant physical impacts, and the time-consuming therapies that impact adherence, there is a critical need for new drugs and therapies for those impacted by this debilitating and deadly disease.

Meeting Design

CFRI began planning the Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis in August 2017, when it submitted its Letter of Intent to the Food and Drug Administration. CFRI and its organizational partners believed that there was a need and urgency for this meeting due to the disease's complex symptoms, fatal consequences and lack of a cure. In light of new therapies in development, it was vital to formally and systematically capture patients' perspectives on clinical meaningfulness. Through the Externally-Led PFDD, CFRI hoped to hear from those who have current access to new therapies as well as those waiting upon therapies in the pipeline. It was CFRI's belief that a more robust understanding of the patient's perspective on meaningful change in overall health was urgently needed, and that knowledge of the patient perspective by all parties involved in the drug development and review process would bring focus and efficiency to future drug development and regulatory review activities.

The meeting goals and objectives for the meeting were as follows:

- To enhance understanding on learnings captured in CF community surveys on the patient perspective on burden of disease, adherence issues and improvements that may be gained through potential treatments.
- To enhance understanding on learnings captured in CF community surveys from the individual with CF's perspective on life with the newest therapies aimed at halting the progression of the disease.
- To expand and increase the breadth of people with CF engaged in defining benefit-risk considerations from the perspectives of people with CF across the varying degrees of the CF health spectrum, as this has not been formally explored for CF.
- To contribute meaningfully to the advancement of the development of treatments for CF through collaborative, systematic engagement of people with CF and their caregivers.
- To explore and enhance opportunities between individuals with CF and biopharmaceutical companies regarding input from the perspective of people with CF on conducting clinical trials.
- To enhance understanding on the unique needs and available therapeutic options for post-lung transplant individuals with CF.

The meeting was held on October 29, 2018, in Hyattsville, Maryland, from 9:45 am to 3:15 pm EST, so as to facilitate participation by representatives of FDA. The meeting had been marketed to the national CF community through CFRI's email list of over 17,000 constituents, and postings on CFRI's website and social media sites. CFRI's partners in the Cystic Fibrosis Engagement Network, including the Boomer Esiason Foundation, Emily's Entourage, Rock CF Foundation, Bonnell Foundation, and CF Lifestyle Foundation, all promoted the meeting to their constituents, as did Attain Health, Cure CF, and the Cystic Fibrosis Foundation.

The meeting was moderated by James Valentine, JD, MHS, of Hyman, Phelps and McNamara, P.C. Mr. Valentine worked as a patient liaison with the FDA for several years, and since that time has facilitated numerous Externally-Led Patient Focused Drug Development Meetings for other rare disease communities. Invitations were extended to officials at the FDA, and CFRI was honored to have Robert Lim, MD, from the FDA's Division of Pulmonary Allergy and Rheumatology Products in the Center for Drug Evaluation and Research, to provide opening remarks. Tejashri Purohit-Sheth, MD, Director of the Divisions of Clinical Evaluation and Pharmacology/Toxicology in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research at the FDA generously provided closing summary remarks, which movingly incorporated the comments of panelists and participants. Other members of the FDA attended in person, as well as remotely.

Panelists were selected to represent both the pediatric and adult populations, as well as to provide representation from across the United States, including California, Montana, Pennsylvania, Michigan, Kentucky, Tennessee, New York, and Delaware. NFL star and CBS football commentator Boomer Esiason, whose son Gunnar has CF, welcomed meeting attendees in a recorded statement. CFRI's executive director provided opening remarks to launch the day's meeting.

Due to the risk of cross infection between adult panelists with CF, several panelists called in to make their statements and participate in the discussion.

In order to expand participation to the national cystic fibrosis community, as well as to address cross-infection risks, the meeting was live streamed. CFRI had sent the log in information to everyone who had previously registered to attend, and then posted the link on its website. Remote attendees were able to watch the meeting in real time, and were invited to share their comments during the group discussion periods via telephone or email.

At the conclusion of the event the recording of the meeting was posted on CFRI's YouTube channel, with an invitation to respond to the polling questions. CFRI also notified its constituents that they would be able to email comments for inclusion in the Voice of the CF Patient Report (Appendix 7). Due to the meeting's early start on the East Coast, many individuals with CF on the West Coast were unable to attend the morning session. An additional 350 watched the meeting post-event, with 61 individuals participating in the polling. Because a greater percentage of respondents post-event were individuals with CF or their parents, their responses will be incorporated into this report.

On the day of the event, over 50 people attended in person, while an additional 364 people watched online. After opening remarks were provided, James Valentine took over as facilitator, reviewing the goals and objectives for the day, and overseeing live demographic polling. The live polling provided a valuable tool for instantaneous input from those in the room and those watching the meeting online.

The day was divided into morning and afternoon sessions. The morning program addressed "Disease Symptoms and Daily Impacts that Matter Most to Patients with Cystic Fibrosis or Their Parents." Questions posed to draw comment included, "What symptoms of CF have the greatest impact on your life? How do symptoms impact your (your child's) daily life? What worries you most about your/your child's condition?" A panel of four parents of children with CF shared their experiences and perspectives, followed by a panel of four adults with cystic fibrosis. After hearing from the panelists, the moderator facilitated a group discussion that incorporated panelists, as well as participants in the room and online.

During the afternoon, a panel of four parents of children with CF, and a panel of four adults with CF addressed topic #2: "Perspectives on Current Approaches to Treating CF; Goals for Potential Treatments; Drug Development Issues." Questions posed included, "What are you/your child doing to help treat CF and its symptoms? What are the most

significant downsides to current treatments, and how do they affect your daily life? Have you/your child participated in a clinical trial? Would you participate in a clinical trial that did not include a placebo?" As with the morning session, James Valentine facilitated a group discussion that incorporated the experiences of the diverse event participants.

Demographics of Meeting Participants

Of the over 415 meeting attendees, 141 participated in the demographic live polling the day of the event. Of these respondents, 30% were immediate family members of a person with CF, while 19% were individuals with CF. Sixteen percent of attendees were representatives of medical equipment of biopharmaceutical companies, while the remaining attendees were CF clinicians, researchers, government employees, or advocacy group representatives. Polling of those who watched the meeting in the 30 days after the event led to 61 responses, 52% of whom were individuals with CF, and 46% of whom were immediate family members of those with CF. Respondents to both polls were predominantly female with 80% indicating they were female.

On the day of the meeting, the majority of respondents indicated that they resided in the Eastern Standard Time Zone (55%), followed by Pacific Standard Time (24%), with the remaining distributed between Mountain and Central Time Zones. This distribution of participants held true for those who responded to post-meeting polling.

Respondents were more likely to live in a city (44.4%) or in a suburban are (37.4%) than a rural area (18.2%). Because individuals with cystic fibrosis are strongly encouraged to receive their care at a Cystic Fibrosis Foundation accredited CF center, many individuals must travel long distances to reach their care team. While 48% of respondents traveled less than 25 miles to their CF center, 17% traveled 25 to 50 miles, while 35% traveled more than 50 miles for their CF care.

Health insurance is a vital issue for the cystic fibrosis community. Of the 106 individuals with CF and/or their family members responding to the poll, 30% had coverage though state Medicaid/Medicare, 41% through their or their family member's employer, and 29% though private insurance.

Topic 1: Disease Symptoms and Impact on Quality of Life

Cystic fibrosis impacts multiple organ systems and its symptoms are diverse. Two panels addressed the first discussion topic, exploring the impact of the multiple and often debilitating symptoms of cystic fibrosis, and their impact upon daily life. The first panel was comprised of four parents of children with cystic fibrosis, while the second was comprised of four adults living with the disease.

Parent Panel

Panelist 1, **Kat**, mother to Maylie, 12 years old with CF, shared that her daughter "grapples with four co-morbid diagnoses: peripheral neuropathy, asthma, GERD, and cystic fibrosis-related diabetes… Maylie lives a life that begs her to be strong, in a body that continually fails her."

Panelist 2, **Jen**, mother to 16-year-old Michael, has watched her son miss out on sports and activities, due to frequent lung infections, and three to six hospitalizations per year. "He has missed out on playing sports he wanted to play because he was too sick or too little. He still has regrets of never being able to play football. He was so skinny and with so many hospital stays it was just not something he could do."

Panelist 3, **Joey**, father to Luke, 11 years old with CF, talked about Luke's challenges with mucus build up, pancreatic insufficiency, hyponatremic dehydration, and liver complications. "My biggest job or responsibility is making sure that… Luke outlives me."

Panelist 4, **Jane**, shared that her 7-year-old daughter, Hannah, nearly died at birth due to meconeum ileus – an intestinal blockage – that caused her intestines to rupture. With no family history of cystic fibrosis, it was a shock to hear the CF diagnosis. "My joy and relief quickly turned to grief and fear."

Adult Panel

Panelist 1, **Emily K-G**, 33 years old, discussed her advancing lung disease, including a recent pneumothorax (lung collapse), which has limited her ability to pursue many life activities. She has a nonsense mutation and there are no current innovative therapies available to slow her disease progression. "CF, you take my breath, you take my friends, you take my dreams of a career and a family, you take my hope, my promise, my very potential. You take my future, and now you take my joy."

Panelist 2, **Gunnar**, 27 years old, shared his extreme challenges with the three pillars of CF – respiratory, gastrointestinal and mental health. Battling multi-drug resistant pathogens that have colonized his lungs and required over 20 rounds of IV antibiotics in the past 5 years, he has experienced painful pancreatitis, nutritional challenges, and mental health issues. "Is it shocking that years of medical trauma and declining health have elicited feelings of anxiety, stress, despair, loneliness, and pressure?"

Panelist 3, **Lise Courtney**, talked about the time-consuming morning medical regimen she must follow without fail every morning which requires up to three hours to complete. She does so without fail: "My life relies on it."

Panelist 4, **Emily S**, 36 years old, shared that once she reached her teen years, the lung infections increased dramatically, leading to long hospital stays, missed school, and the loss of activities she loved. "Truthfully, I was scared about my health and if I had a future, because I was sick so much and my friends with CF from camps and the hospital were passing away."

The panelists' full statements can be found in the Appendix.

To expand the discussion, meeting participants with CF/family members of those with CF were asked questions via live polling, after which James Valentine moderated a group discussion involving panelists, and attendees in the room and those participating remotely.

Participants were asked, ***"Which of the following CF-related symptoms do you or your loved one cope with on a regular basis?"*** (Include all that apply.)

As shown in the following results, the top three symptoms noted by respondents were gastrointestinal issues, pulmonary exacerbations/infections and excessive cough. Of note are the high percentages associated with multiple symptoms of the disease, including to GI, pulmonary, sinus, and mental health issues as well as fatigue and shortness of breath.

Which CF-related symptoms do you/your loved one cope with on a regular basis?

Disease Symptoms In Order of Response	Percent	Rank
Gastrointestinal Issues	74%	1
Pulmonary Exacerbations//Infections	72%	2
Excessive Cough	65%	3
Sinus Disease	59%	4
Mental Health Issues	58%	5
Fatigue	58%	5
Shortness of Breath	57%	6
Tight Chest	38%	7
CF-Related Diabetes	33%	8
Chronic Pain	32%	9
Liver Disease	7%	10

103 Responses

When asked, ***"How has the impact of your/your loved one's cystic fibrosis changed over time?"*** 77% of poll respondents at the meeting said, "Impact has gotten greater or affects additional areas of our life (home, school, work, friendships, intimate relationships, etc.); 14% said that the impact remained the same; 7% felt that the impact had lessened. In light of the new therapies that have become available in recent years, and the accompanying increase in life expectancy, it is important to note that the impacts continue to increase over time for the vast majority of respondents.

Meeting participants with CF/family members of those with CF were asked:
"Of the symptoms you cope with, what are the 4 issues that most significantly impact you or your loved one's quality of life?" As shown in the following results, the top three symptoms noted by respondents were pulmonary exacerbations/infections (1); excessive cough (2); and gastrointestinal issues (3).

Symptoms That Most Impact Quality of Life	Percent	Rank
Pulmonary Exacerbations/Infections	69%	1
Excessive Cough	48%	2
Gastrointestinal Issues	47%	3
Fatigue	39%	4
Shortness of Breath	37%	5
Mental Health Issues	33%	6
Sinus Disease	32%	7
CF-Related Diabetes	21%	8
Chronic Pain	18%	9
Tight Chest	10%	10
Liver Disease	1%	11

102 Responses

Pulmonary Exacerbations/Infections:

Progressive lung disease leading to respiratory failure is the primary cause of death for those with cystic fibrosis. Due to the thick, sticky mucus in the lungs, individuals with cystic fibrosis are vulnerable to opportunistic pathogens

that damage the airways. Patients with CF are likely to culture (and often be colonized with) hardy bacteria such as *Pseudomonas aeruginosa, Staphylococcus aureus, Stenotrophomonas maltophilia, Burkholderia cepacia, nontuberculous Mycobacteria*, and/or other bacteria. Exacerbations – lung infections often accompanied by fever, a drop in lung function, fatigue, weight loss, and/or hemoptysis – are treated aggressively, often requiring hospitalization and IV antibiotics. But after years of intensive antibiotic use, many individuals develop allergies to specific antibiotics, or the pathogens become resistant. The physical and mental impacts of this are significant.

> *As my exacerbations increased each year I developed allergies to almost all of the antibiotics that treat Pseudomonas. This required me to stay inpatient for 2 to 4 weeks each time to make sure I could tolerate the drugs. Aside from Pseudomonas I started to culture MRSA and Stenotrophomonas on and off. As my infections increased, my lung function and exercise tolerance began to drop. In my early 20s I went on social security/disability because I could no longer work full time.*
>
> *– Emily S, 36 years old*

> *I'm dealing with multi-drug resistant bacteria in my lungs. And with that, my antibiotic arsenal is so limited by virtue of a number of allergies, but also antibiotic resistance. There's only a handful of things that actually work, whether I'm inhaling something that is for off-label use only and we're kind of just guessing as we go, or something that is really known to kind of work or something we're really just hoping works. I get fevers, I'm inflamed, I have fatigue issues. When my infection is flaring up and I'm in the middle of a pulmonary exacerbation, my appetite drops and I'm dependent more so on my feeding tube.*
>
> *— Gunnar, 27 years old*

> *My son has had many of the complications already mentioned: meconimum ileus surgery, 28 courses of intravenous antibiotics, multiple PICC lines, broviac, port-a-cath, many line complications, chronic colonization with MRSA, NTM infection, etc.*
>
> *— Laura, mother to a 22-year-old son with CF*

> *Michael was facing a long-term treatment for bacteria he has in his lungs. It's one of the bad ones, called AFB (acid-fast bacilli). This treatment would mean up to 9 - 12 months of IV antibiotics, which come with all sorts of side effects including hearing loss (we've heard that around 80% of those with the treatment end up with hearing aids). Liver failure is also a potential side effect. Michael asked for "a kick ass summer" before we would begin. He wanted one last summer to not be hooked up to IVs, one last summer to have his hearing, and one last summer to feel like a kid.*
>
> *— Jen, mother to Michael, 16 years old with CF*

Declining lung function, pneumothorax, and hemoptysis are often caused by opportunistic pathogens as well as chronic inflammation. Pneumothorax occurs when, due to advanced lung disease, air leaks from the lung into the chest cavity. That air presses upon the lobes, causing the lung to collapse. One panelist spoke compellingly of her shock to find that she was experiencing a lung collapse, despite strict adherence to her medical regimen.

> *I remember sitting outside the Pearlman Center for Advanced Medicine when I got a call that changed everything. "Emily," he said with alarm, "Your x-ray revealed that your lung is partially collapsed in three places." I remember hanging up the phone, looking up at the big blue sky, and then back down at my body, stunned that a body so seemingly functional could be so secretly broken.*
>
> *— Emily K-G, 33 years old*

While half of adults with CF will have episodes in which they see streaks of blood in the mucus they cough up, it is estimated that between 5% and 9% of adults with CF will have a massive hemoptysis that leads to coughing up over a cup of blood in 20 minutes. Massive hemoptysis can be fatal. The sensation of drowning, and the trauma of coughing up blood can have lasting impacts upon CF patients' mental health. Because these bleeds can happen with no warning, those who have experienced them often have high anxiety that it will occur again.

I've been dealing with massive hemoptysis for a great part of my life… This impacts me tremendously, because as anyone who's experienced coughing up blood, it can sometimes happen out of the blue… I can experience episodes ranging from maybe two tablespoons to maybe a quarter or even a half cup anytime between 20 and 30 times a year… I'm on disability currently despite absolutely loving my job.

— Amy, 37 years old

I was diagnosed with cystic fibrosis, along with my identical twin sister Ana, at birth. Despite our obsessive compliance, a downward progressive spiral of lung infections eventually destroyed our lungs. I coughed up blood regularly and nearly died from two massive hemoptysis episodes; bronchial arterial embolizations saved my life. We could no longer wait for additional drugs. Transplantation was our only hope.

— Isa, 46 years old with CF

Excessive Cough:

Individuals with cystic fibrosis must cough to clear the thick mucus from their airways, but for some it becomes an exhausting and uncontrollable activity. In addition to the mucus in the lungs, coughing may be triggered due to post-nasal drip from chronic CF-related sinus disease. It may also be a result of reflux, a common issue for people with cystic fibrosis. The coughing can significantly interfere with sleep, cause back pain, displace ribs, use precious energy, reduce appetite, and interfere with respiratory therapy. It can also draw unwanted attention in public and stigmatize individuals with CF.

Every morning I wake up and I start with what I like to describe as my morning coughs. After having rested all night, my lungs have settled, and with that the mucus has built up and settled into my airways. Waking up in the morning requires that my lungs also wake up through a long process of coughing. Sometimes the coughing is so intense that it triggers my gag reflex and causes me to throw up.

— Lise Courtney, 24 years old

Every cough that comes from Natalie sounds scary and reminds us that there is something very wrong in her body. They say that having cystic fibrosis is like drowning from the inside. Well, as Natalie's dad, the feeling I have is like watching my daughter drown while being behind the fence that is far too tall for me to get over.

— Arek, father to Natalie, 4 years old with CF

My daughter has a chronic cough. There is a self-consciousness in standing out constantly… but it's also that she doesn't sleep well because she's coughing through the night. She's literally displaced her ribs from coughing so hard, which is excruciatingly painful and impacts respiratory clearance. This has been a hard thing for her, pretty much her whole life.

— Siri, mother to Tess, 23 years old with CF

Gastrointestinal Symptoms:

Gastrointestinal issues ranked among the top two problematic disease symptoms experienced by those with CF. During the morning panelist presentations, these symptoms were referenced frequently. This response may come as a surprise to many, as cystic fibrosis is most often identified as a respiratory disease. These survey results indicate that patients with CF need therapies that address their GI issues, which may include problems with absorption, nutritional deficits, blockages, and daily GI discomfort. Management may include enzyme replacement therapy, enteral feeding (G-tubes), supplements, and sometimes, surgery.

Meconium ileus occurs in nearly one out of five babies with cystic fibrosis. Meconium is the first stool passed by a baby. Because CF causes fluids and mucus to be thicker, the meconium becomes lodged in the ileum, leading to an intestinal blockage. If not discovered in time, the intestine can be perforated or rupture. Surgery is usually required to remove the obstruction. Prior to newborn screening, the presence of meconium ileus was often the key to a cystic fibrosis diagnosis.

When I was born I had meconium ileus- which is a bowel obstruction that required emergency surgery. I have giant scars across my stomach - from not only the surgery but the two colostomy bags I had for the first 6 months of life. I had blockages when I was younger that caused long hospital stays. My daily regime to curb my chronic stomach pain and discomfort includes 6 medications. I have lost count of the amount of time I have missed from work, school or social functions because of my digestive issues.

— Anna, 31 years old

My family's journey with CF began soon after Hannah's birth… We learned that Hannah's intestines had ruptured during birth and she nearly died. At the time I had no idea that this was called meconium ileus, a blockage of the intestines which is a common sign of cystic fibrosis.

— Jane, mother to Hannah, 7 years old with CF

The pancreas is one of the most commonly affected organs in those with cystic fibrosis. The decreased production of bicarbonate leads to thick and dry pancreatic secretions, ultimately plugging the pancreatic ducts, and blocking the release of pancreatic enzymes into the intestine to aid in the digestion of food. Despite the blocked ducts, the pancreas continues to produce enzymes, which ultimately damage the pancreatic tissue. As a result, most CF patients must take enzyme replacement therapy so as to digest their food and absorb nutrients. Even with replacement enzymes, malabsorption is common, impeding vitamin absorption, and causing weight loss, diarrhea, and malnutrition. Another complication is pancreatitis, an inflammatory process that causes extreme abdominal pain, vomiting, and diarrhea.

My gastrointestinal health has suffered the wrath of cystic fibrosis. In 2010, I suffered from pancreatitis, an incredibly painful and debilitating complication of CF. To treat my pancreatitis I had to withhold food and drink for several days, before slowly advancing my diet back to normalcy. During that time my weight dropped close to 130 pounds. I am 6 foot 3; I was skin and bones. In the months that followed, I had a feeding tube placed, and in no small way, my G-tube saved my life.

— Gunnar, 27 years old

Fatigue:

Fatigue is a constant symptom for many with cystic fibrosis. There are numerous reasons for this, including the energy required of the body to fight chronic infections, exacerbations, chronically interrupted sleep, and nutritional challenges. As shared by Somer, 39-year-old woman with CF, whose lung function hovers at 27% of predicted and who relies on oxygen supplementation 24 hours per day, "I literally think about every breath I take. CF is not easy, it is inconvenient, and it can be very exhausting." Of those responding to the polls, fatigue was listed sixth out of 11 symptoms that must be coped with on a regular basis. When asked which symptoms significantly impact quality of life, fatigue was listed third by those attending the event, and fourth by those responding to the post-event poll.

I left for work two hours after waking up, (so as) to do my treatments and eat a nutritious breakfast, I was completely exhausted from coughing and felt like the days I went to work I was severely fatigued before ever arriving.

— Jessica, 29 years old

Fatigue: With my body constantly fighting two to three strains of staph—depending on the culture —I am chronically exhausted. Some days, I sleep for up to 13 hours because I am so tired. This has impacted my day-to-day life, as I feel too tired and/or weak to leave the house half of the time.

— Tess, 23 years old

Mental Health Issues:

Individuals with cystic fibrosis and their loved ones have rates of depression and anxiety that are two to three times higher than those of the general public. Living with a chronic and fatal disease creates stress and depression that has little relief. Many meeting participants discussed their fear of worsening lung disease and death, and the pain of

losing their fellow friends with CF. Many noted that CF is a capricious disease, and that despite adherence to their medical regimen, they had experienced serious complications, including life-threatening infections and hemoptysis. This leads to a constant sense of anxiety for many, waiting for an unexpected catastrophic health event. Many mentioned experiencing symptoms of post-traumatic stress.

> *Regarding mental health, by age 3, my son was cursing out CF and we could no longer get him in the car for procedures. He's 14 now and has had 40 surgeries...24 sinus surgeries, 10 PICC lines, 2 port surgeries and others. It's a disaster. He was diagnosed with PTSD (post-traumatic stress disorder)…*
>
> *— Megan, mother to Aidan, 14 years old with CF*

> *Sonya came out of the museum gift store in Madrid and had a massive life-threatening hemoptysis. She felt a sudden rush in her chest, and then felt like she was drowning. She stresses that the mental health component is completely interwoven with the physical impacts of the disease… because it is so capricious; there seems to be no rhyme or reason. So part of it is living in fear when you have had an experience like this. She truly feels she has post-traumatic stress disorder, from the trauma of it.*
>
> *— Siri, conveying a message from Sonya, 43 years old*

Individuals with CF have experienced a lifetime of medical interventions, often have the sense that one has no control despite hours invested daily in one's medical regimen, and are increasingly isolated due to cross infection risks. Individuals with CF are discouraged from interacting in person, and when they are together, to maintain a minimum of six feet between them. Those culturing pathogens that are particularly hard to treat, such as those belonging to *Burkholderia complex, nontuberculous Mycobacteria* or, or methicillin-resistant *Staphylococcus aureus*, are usually prevented from attending any CF-related events. This has led patients to feel isolated, and for some, "like a leper." While social media and online platforms are frequently utilized to create connection between those with cystic fibrosis, it is emotionally challenging to be unable to freely socialize, meet for support groups, and participate together in life activities.

It is increasingly understood that depression and anxiety symptoms interfere with adherence to one's medical regmen. Access to mental health support services is vital.

> *My mental health went overlooked for far too long. Prior to a few years ago, no one had ever thought to ask me how I feel about cystic fibrosis. Outside of casual conversation with my doctor during appointments, no one inside the clinic stopped to ask what it was like to be in the midst of more than 20 pulmonary exacerbations. Why? It's because we do not have the proper tools to treat and support cystic fibrosis patients dealing with mental health issues.*
>
> *— Gunnar, 27 years old*

> *It is a horrible feeling knowing that your body is failing you. I can feel the decline. The impact the progression of this disease has on me physically can be measured by FEV1 scores and BMI charts, but the impact it has on me mentally is hard for others to comprehend. CF is a challenging and isolating disease. I have lost many friends to this illness. This takes a toll on me. I now see a psychologist to help treat the impact CF has on my mental health.*
>
> *— Anna, 31 years old*

> *The hospital visits and the doctor visits are… extremely stressful for everyone involved, especially for a 4 1/2 year-old. We have to do annual (blood) labs. The labs for a 4-1/2 year-old take about a minute. That minute feels like three hours, or as one of my friends likes to say, "Two minutes while on fire."*
>
> *— Arek, father to Natalie, 4 years old with CF*

Sinus Disease:

Sinus disease impacts the majority of individuals with cystic fibrosis. The cells lining the sinuses mimic the cells lining the lower airways; as such, the issues with inflammation and thick mucus are the same. Sinus disease causes painful head-

aches, a chronic post-nasal drip that exacerbates coughing. The post-nasal drip may lead to inadvertent swallowing of the mucus, which causes nausea and diminished appetite. Many individuals develop nasal polyps that block off the sinuses cavities and create inaccessible pockets of infection. These polyps must often be removed surgically, and there are many individuals with CF who have had multiple sinus surgeries.

> *I have had sinus issues my entire life. I have had five sinus surgeries, all of which have been scary and painful. Despite flushing my sinuses and using nasal steroids, the polyps always recur, and I have a constant post-nasal drip, which makes me cough incessantly to the point of gagging, and makes my voice hoarse.*
>
> *— Tess, 23 years old*

Cystic Fibrosis-Related Diabetes (CFRD):

The damage to the pancreas described earlier causes many with CF to develop cystic fibrosis-related diabetes. CFRD is increasingly diagnosed due to improved screening, impacting over 40% of adults. In addition to complications related directly to diabetes (extremely high and low blood glucose levels, diabetic retinopathy), those diagnosed with CFRD are more likely to have reduced lung function, poorer nutritional status, and an enhanced vulnerability to lung infections (Kayani et al, 2018). Due to the use of corticosteroids and immunosuppressive therapy post transplant, it is estimated that nearly 75% of individuals with CF will develop CFRD after their double-lung transplant (Lynch, et al, 2015). Even with excellent management of blood sugars, those with CFRD face increased likelihood of earlier death than their peers without diabetes. The challenges of glucose management and the associated symptoms of CFRD create another significant daily challenge for those with CF.

> *I think what is so challenging about CF-related diabetes is that because your insulin needs are constantly changing, because they're so dependent on my lung health, it's really hard to get your CF related diabetes in tight control without also risking lows, which can be life threatening. It sometimes feels like a losing proposition.*
>
> *— Emily K-G, 33 years old*

> *My CF-related diabetes is my greatest daily struggle with blood sugars between 40 and 350.*
>
> *— Isa, 46 years old, post-transplant*

Chronic Pain:

While chronic pain ranked lower on the list of symptoms that impact quality of life, many individuals with cystic fibrosis live with chronic pain due to a variety of causes. Excessive coughing can displace ribs and throw out backs. CF related arthritis, chronic headaches from sinus disease, gastrointestinal cramping, and the after-effects of pleurodesis are only a few of the sources of pain, and many individuals experience these simultaneously.

> *I suffer from CF related arthritis. Sometimes my arthritis is so bad that it is excruciating for me to type, but I have to push through because I don't want to waste a sick day on my hands hurting.*
>
> *— Lise Courtney, 24 years old*

> *Maylie lives a life that begs her to be strong, in a body that continually fails her. The idea of resilience in cystic fibrosis is the supreme illustration of irony; you need reprieve from pain in order to find resilience, do you not?*
>
> *— Kat, mother to Maylie, 12 years old with CF*

> *I deal with early onset arthritis, pancreatic insufficiency and sinus infections. Each day I deal with pain, just on differing levels.*
>
> *— Jennifer, 53 years old*

Topic 1 Continued: Challenges Created by a Cystic Fibrosis Diagnosis

The multiple and diverse symptoms of cystic fibrosis create many challenges for those living with the disease. Long hours spent doing daily respiratory therapy, multiple clinic visits, frequent hospitalizations, lung infections, low lung function, dependence on oxygen, depression, anxiety, and many other challenges lead to difficulties attending school or work, or participation in social and extracurricular activities.

Participants were provided with a list of activities, and asked:

"Select the three most important things you or your family member with CF have found to be more challenging because of your/his/her diagnosis with cystic fibrosis."

The results were as follows:

Activity	Percent	Rank
Spending time with friends/participation in social activities	67%	1
Attendance at work or school	54%	2
Participation in sports or extracurricular activities	56%	3
Maintaining financial stability	36%	4
Other	24%	5
Finding/Keeping a job	22%	6
Performing well at school or work	16%	7

100 Responses

Spending Time with Friends/Participation in Social Activities:

The tremendous investment of time required for treatments, chronic fatigue, sinus and lung infections, and regular hospitalizations – all interfere with time available to spend with friends and enjoying social activities. So, too, does the fear of infection at group events. This is not limited to cross infection risks between individuals with cystic fibrosis. While those without CF may be known to say, "It's only a cold," those living with CF understand that this virus could lead to a spiral of infection that leads to IV antibiotics and hospitalization. For adults with cystic fibrosis, hard decisions must be made about what events are options to attend. For parents of children with CF, there is the concern of putting their children at risk. This concern often conflicts with their desire for their children to have a "normal" childhood, thereby adding to their emotional stress.

> *We try to maintain a version of normal, but that is virtually impossible. A much-anticipated day at the trampoline park: a distant cough is heard, all eyes on alert as we scan for the potential predator to our outpatient life. We see the child; the day is aborted. Nothing is worth the risk of our family being separated for yet another hospitalization.*
>
> *— Kat, mother to Maylie, 12 years old with CF*

> *The biggest challenges we have with Luke and cystic fibrosis stem from his mucus buildup and resultant infection. As a result of this, Luke does not attend sleepovers with his 6th grade classmates. Just recently Luke had a "sleep under" where we came and picked him up around 11:00, while the other classmates stayed and enjoyed the rest of the night.*
>
> *— Joey, father to Luke, 12 years old with CF*

> *What should be fun becomes stressful: should I let her go to the birthday party if I think another child is sick? What is worse – her getting sick, or her feeling isolated and different? This is our norm, our everyday, racking our minds over every little decision, questioning if it was the right one.*
>
> *— Jane, mother to Hannah, 8 years old with CF*

Participation in Sports or Extracurricular Activities:

As with spending time with friends and participation in social activities, many individuals with CF are unable to participate in sports or extracurricular activities due to respiratory infections, fatigue, shortness of breath, frequent hospitalizations that interfere with practices, and concern that participation will cause harm to PICC lines and ports.

> *Many times he could hear his friends outside playing, but he was just too sick to go so he would stare at the window. He would ask me "Why? Why do I have CF, mom?" A question to this day I still cannot find the right words to answer.*
>
> *— Jen, mother to Michael, 16 years old with CF*

Maintaining Financial Stability:

For many individuals and their families living with cystic fibrosis, financial stability is a challenge. For parents of those with CF, medical appointments require frequent time off from work, often with lost wages. For individuals with CF, depending on disease symptoms, severity and progression, maintaining a full-time job may be a challenge.

> *I remember on October 16, 2017, I was a full-time high school teacher, department chair, and involved in many committees within my building. Less than 24 hours later I became severely ill and was hospitalized. My initial thought was, "hey, I need to be out by Friday morning, I'm a bridesmaid in my friend's wedding, give me some IV antibiotics and let me get back to my job, my house, my life," but within a couple of days (I) had to be transferred to ICU in respiratory failure.*
>
> *— Jessica, 29 years old*

> *When my son started working full time at his next job, his health suffered and he had to quit and has since gone back to online school. Last year he was on intravenous antibiotics for a total of 4 months. The treatment burden with this disease is so high that in order to adequately manage one's health, working full time is not really an option for most. People do it, but there is a price to pay.*
>
> *— Laura, mother to a 22-year-old son with CF*

Patients with CF require frequent medical interventions and care from numerous specialty areas, including pulmonary, gastroenterology, otolaryngology, transplant, and endocrinology. Medical equipment – e.g. the mechanical vests, and compressors necessary for respiratory therapy – adds to the cost. In addition, there are many other expenses related to CF care that must often be paid out-of-pocket, such as vitamins, nutritional supplements, sterile wipes, and sterilizing equipment for nebulizers.

> *I love my job, but I am constantly asking myself if I can keep up… Long nights at work for me mean that I am losing valuable sleep that helps me fight off infections and stay alive. But not succeeding at work means losing the ability I have to pay for medications through the strong health insurance program my employer has.*
>
> *— Lise Courtney, 24 years old*

Maintaining health insurance is often key to financial stability, as the cost of CF care and prescriptions is extremely high. As reported earlier, nearly a third of meeting participants had coverage though state Medicaid/Medicare, 41% through their or their family member's employer, and 29% though private insurance. Medication costs are extremely high (CFTR modulator drugs alone cost approximately $300,000 per year). Maintaining health coverage is a significant source of stress for many individuals with CF and their family members.

> *Our insurance premium is $43,000 per year. It's a pricey, pricey disease on top of everything.*
>
> *— Arek, father of Natalie, 4 years old with CF*

> *I am so relieved to be on my parents' health insurance plan, but in two years I turn 26 and I stress about what I will do.*
>
> *— Tess, 23 years old*

Attendance at Work or School:

Many individuals miss school and work due to health complications related to CF. This can be due to exacerbations that cause fevers, extreme coughing, fatigue, and which necessitate additional therapeutic interventions, including hospitalizations and IV antibiotics. Digestive issues were frequently cited as causing absences from school and work. Numerous participants mentioned having to drop out of school, forego career plans, and leave work to go on disability due to their disease. Many expressed concern that their employers would pass judgment on them due to their absences. For those dependent on their employer's health insurance plan, the stress of losing coverage can cause individuals with cystic fibrosis to postpone taking sick days in fear of jeopardizing their position.

> *In addition, explaining CF to an employer is a daunting task to say the least. You risk your employer believing you're not capable and unfortunately, sometimes I think they are right. The truth is that I am out sick more often, I go to the bathroom far more frequently, and I tire more quickly than my coworkers.*
> *— Lise Courtney, 24 years old*

> *I have lost count of the amount of time I have missed from work, school or social functions because of my digestive issues.*
> *— Anna, 31 years old*

> *I was so sick through high school and college – multiple rounds of IV antibiotics and a couple sinus surgeries. In college, I always worked with the Office of Disabled Student Services because inevitably I would get sick and fall behind in my classes. At one point I had to drop out for a semester.*
> *— Tess, 23 years old*

Having identified many of the challenges experienced by those living with cystic fibrosis, meeting attendees were asked to identify what issues cause them the most stress. Through live polling, meeting attendees were asked to, ***"Select the top three issues that worry you/your loved one most about life with cystic fibrosis."***

The responses were as follows:

Issues That Worry You About Life with CF	Percent	Rank
Advancing lung disease	81%	1
Death	44%	2
Social Isolation	35%	3
Transplant	34%	4
Mental/Emotional Health	32%	5
Ability to live independently	31%	6
Finding a Job/Career Success	20%	7
Physical Pain	15%	8
Other	6%	9
Academic Success	4%	10

100 Responses

For all those who responded to the polls, advancing lung disease was far and above the most common worry. Lung function decline is the consistent trend for most individuals with CF, and this decline leads to other issues – death, transplant, social isolation and mental health issues, the need for oxygen, and the inability to live independently.

Advancing Lung Disease/Death:

Regardless of age, most individuals expressed concerns about advancing lung disease and death. While complications such as CFRD, or low BMI can wreak havoc upon lives, respiratory failure remains the primary cause of death for those with cystic fibrosis. With the median age of death from complications of CF still at 30 years, many adults with CF participating at the meeting have lost friends and peers to the disease. The sense of loss and fear this causes was compellingly shared.

I have anxiety about infections, about dying, but more about how my family will deal with my death.

— Jessica, 29 years old

Truthfully I was scared about my health and if I had a future because I was sick so much and my other friends with CF from camps and the hospital were passing away.

— Emily S, 36 years old

Parents expressed their struggle to balance hope for their children, but also their deepest fear that they will lose their children to CF.

I want Hannah to be whoever she wishes to become. My fear is that she will never get the chance to fulfill those dreams – for her never to be a vet, never having a chance of love, or becoming a mom. How destroyed Grayson (her brother) will be if his partner in crime is no longer around. Some dream of winning the lottery. My jackpot would be having Hannah outlive me.

— Jane, mother to Hannah, 8 years old with CF

I see hope, but the fear is still there, every day. The fact remains we have no cure or long-term treatments.The fact is CF will take my son still at a very young age. In one of our most difficult conversations around life expectancy, Michael said to me, "Mom do you know what my biggest fear is?" I said, "Is it losing the battle to CF?" He said, "No, it's dying without ever knowing what a normal childhood should feel like."

— Jen, mother to Michael, 16 years old with CF

Social Isolation:

As described earlier, the cross infection risks that exist between people with cystic fibrosis keep individuals isolated from one another. This is worsened when an individual cultures a particularly virulent pathogen, such a *B. cepacia*. Many individuals with CF express the sense that others do not understand the challenges that they cope with on a daily basis. High rates of depression and anxiety, the inability to spend time with one's CF peers, and chronic fatigue create a "perfect storm," which reinforces the sense of isolation.

Transplant:

While double lung transplantation has contributed to the growing number of adults with cystic fibrosis, it is an option of last resort, when the inevitability of death from respiratory failure in the relatively near future is clear, or when sudden respiratory crisis necessitates it. While lung transplants can extend lives, and allow many individuals the opportunity to breathe more freely, they are fraught with risks, and create additional potential health complications, including a compromised immune system leading to opportunistic infections, organ rejection (allograft failure), and diabetes. The immunosuppressive medications have side effects, and lead to significantly higher risks of cancer. Many individuals with CF who have had a transplant feel that they have their feet in two worlds; they may have new lungs, but they still have cystic fibrosis along with its related sinus disease, pancreatic insufficiency, and gastrointestinal issues. With transplant comes an additional medical regimen that must be strictly adhered to.

When I was 32, I went into lung failure and was put on a ventilator. The breathlessness and suffering I experienced at the end of my life with CF was something I pray no one else ever has to ever go through. One day after being intubated, I received donor lungs just as I was about to enter a coma. Today, I take 35 medications daily to survive. I am immunosuppressed and have to be very cautious about exposure to germs. Every day I fear rejection, cancer or infection. I have had five skin cancers removed including one extensively spread in my eye. I flush my sinuses daily to limit sinus infections. I endure chronic intestinal blockages and depend on GI motility. I exercise very hard to be an athlete, to celebrate my lungs and to help with bone health, constipation, diabetes and muscle strength. I must monitor my kidney function, as my transplant medications are nephrotoxic.

— Isa, 46 years old

Ability to Live Independently:

Related closely to the concerns about maintaining financial stability, living independently was another source of concern for meeting participants. Living independently can be challenging for many individuals with CF due to the advancing and debilitating symptoms of CF, crushing medical bills, and the challenge of working sufficient hours to pay one's living expenses. For many adults, who must rely on their parents or spouses/partners, this dependence on others impacts self-esteem and contributes to feelings of anxiety and depression.

> *In the months that followed my college graduation, I had to give up my dream of going to law school, I was forced to move back home with my parents, and I was even denied the opportunity to start a career like the rest of my friends until I curbed my decline.*
>
> *— Gunnar, 27 years old*

Many parents of children with CF fear what will happen in the future, should their children be unable to live independently.

> *Natalie's our only child; it's possible we will not have other children. We have to think about not only our own futures and perhaps a retirement, but also design something where we can help Natalie, because as you well know, careers are very challenging, so we must be able to cover her living expenses (and be) able to pay her medical costs.*
>
> *— Arek, father of Natalie, 4 years old with CF*

Reproductive Health Issues:

Reproductive health issues are increasingly salient, as the majority of individuals with CF are now over the age of 18. For both men who are infertile due to the absence of the vas deferens, or women who are unable to conceive, or for whom carrying a child is detrimental to their health, it is challenging to navigate the options available, including assisted reproductive therapies, surrogacy and adoption. As shared by meeting participants, in addition to the physical challenges, there is often an insurmountable financial challenge that forces those with cystic fibrosis to forego their hopes of having a family.

> *In Wisconsin it costs around $50K to adopt domestically and that doesn't take into account that individuals with CF may be "red flagged" or denied based upon our diagnosis.*
>
> *— Jessica, 29 years old*

> *I am not at this stage of life, but many of my female peers with CF have really struggled to conceive, and there is not a lot of research about how CF and reproductive health are linked. When I think about my future, I definitely want to be able to have a family and there's a lot of anxiety surrounding that thought in my mind.*
>
> *— Lise Courtney, 24 years old*

Topic 2: Perspectives on Current Approaches to Treating CF; Goals for Potential Treatments; Drug Development Issues

The treatment of cystic fibrosis entails a complex regimen that requires hours per day to accomplish. There is no cure for CF, and with the exception of the recent CFTR modulator drugs, all therapies have been focused on treating symptoms and complications of the disease. Therapies address airway clearance, infection control, pancreatic enzyme replacement, sinus issues, diabetes, pain, low weight/failure to thrive, gastrointestinal issues, reflux, and inflammation. It is not uncommon for individuals with cystic fibrosis to spend between 2 and 6 hours per day on their medical therapies. Many take numerous medications with precise administration times. It is an extraordinarily burdensome regimen, with no reprieve.

To provide perspectives on current approaches to treating CF, what goals those impacted by CF would have for potential treatments, and their experiences with clinical trials to advance drug development, two panels addressed the meeting. Prior to the meeting, panelists were asked to consider the following questions: "What are you/your child doing to help treat CF and its symptoms? What are the most significant downsides to current treatments, and how do they affect your daily life? Have you/your child participated in a clinical trial? Would you participate in a clinical trial that did not include a placebo?" The first panel was comprised of four parents of children with cystic fibrosis, while the second was comprised of four adults living with the disease.

Parent Panel

Panelist 1, Kat, mother to Maylie, 12 years old with CF, shared how her daughter's life is dominated by procedures and pain. "I live a life defined in numbers… Fifteen hospitalizations since her diagnosis… IV antibiotics consuming over forty weeks of her young life… 8 PICC placements. 2 PH probes. 2 feeding tube placements. 4 bronchoscopies. 2 colonoscopies. 1 endoscopy. 1 port placement. 1 fecal transplant. 1 air flight for peritoneal sepsis… We put in countless hours of therapies, countless drugs enter her perfect, undeserving little body. However, nothing stops the inevitable at this point, so we wait, not too patiently."

Panelist 2, Jen, mother to 16-year-old Michael, described the hours he spends doing respiratory each day, while swallowing over 40 pills per day. "We are in a race against time, and with each new advancement in medication coming to the market we see improvement in Michael's quality and quantity of life. But the fear is still there, every day. The fact remains that we have no cure or long-term treatments."

Panelist 3, Joey, father to Luke, 11 years old with CF, described Luke's daily medical regimen, which requires a minimum of three hours per day and a minim of 13 medications. The burden of care is impacting his son, who is often frustrated during his treatment. "Luke also has rebelled against taking his medications, as his sister, friends and classmates do not take them. He just wants to be normal."

Panelist 4, Arek, shared that his 4-year-old daughter Natalie has a rare mutation for which thee are no new therapies. "Although we're very happy about all the medical breakthroughs that have happened over the last five years, none of them really apply to Natalie. There are no clinical trials currently in place that she would qualify for, and so while we look on with hope, it's a very challenging process."

Adult Panel

Panelist 1, Emily K-G, 33 years old, discussed her advancing lung disease, and her frustration that there are no new therapies for those with nonsense mutations. "There are 7,000 of us still waiting, for whom this disease remains the same killer that it was before 2012. We are the orphans of this orphan disease, still stuck in prehistoric CF times… We are still waiting, yearning, gasping, pleading for something, for anything, so we can hold on."

Panelist 2, Anna, 31 years old, shared that she takes approximately 14,000 pills per year, and spends three to four hours per day on her respiratory therapy (over 1,200 hours per year) to try and slow her disease. An avid participant in clinical trials, Anna participated in the early Orkambi® trial for over a year, despite 4:00 am blood draws, and having to use

vacation time from work. "At no point did I think about giving up on the trial because I knew that this medication could help keep my friends alive longer."

Panelist 3, **Lise Courtney**, 24 years old, has been a participant in numerous clinical trials through the years. "When you talk to me or any other CF patient about what it is like to participate in a clinical trial, it is like we have won the lottery. The truth of the matter is that the reason that CF patients are so eager to give up parts of their lives for medical research is that we are absolutely desperate for a cure or for medications that will improve our quality of life today."

Panelist 4, **Isa**, 46 years old, shared her hopes that new drugs will be developed for CF patient who have received lung transplants, specifically those targeting chronic rejection or bronchiolitis obiterans syndrome (BOS). She added, "I am living proof that ethnic minorities can have cystic fibrosis… We have unique genes and it is my hope that some of the gene-targeted drugs will include mutations that are common in minorities."

The panelists' full statements can be found in the Appendix.

To expand the discussion, meeting participants with CF/family members of those with CF were asked via live polling, ***"What are you/your child currently doing to help treat the condition or its impacts? (Select all that apply)."***

The results were as follows:

Therapy	Percent	Rank
Airway Clearance*	97%	1
Inhaled/Nebulized Bronchodilators	89%	2
Oral Antibiotics	73%	3
Nebulized Hypertonic Saline	95%	4
Pancreatic Enzyme Replacement	89%	5
Nebulized Dnase	78%	6
Inhaled Antibiotics	65%	7
CFTR Modulators	62%	8
Mental Health Interventions	65%	9
IV Antibiotics	43%	10
Insulin	32%	11
Other**	46%	12
Enteral Feedings (G-Tube)	14%	13
None 0%	0	

98 Responses

*Airway Clearance: This includes a mechanical vest that fills with air and provides high-frequency chest wall oscillation (shaking) that helps to clear mucus. Other forms of airway clearance include the Aerobika, Acapella, and Active Cycle of Breathing.

**Other: Includes nutritional supplements for weight gain; vitamins; anti-rejection medications post transplant; antibiotic sinus flushes.

The vast majority of individuals with CF must do some form of respiratory therapy. Respiratory therapy is a time consuming process that is repeated two to four times a day. Depending on the type of compressor one uses (often determined by insurance) and the number and type of medications one must nebulize, the process can take up to two hours each time. Many individuals follow a regimen requiring nebulized bronchodilators to open the small airways, followed by nebulized Dornase alfa, which acts like "scissors" to cut apart the extracellular DNA in mucus, making it thinner and easier to clear. This is followed by nebulized hypertonic saline, which helps to draw moisture to the lungs and hydrate the mucus to make it easier to clear. Lastly, for those culturing specific responsive bacterial pathogens in the airways, inhaled antibiotics (both nebulized and in powder form) are used.

The other most commonly used therapy is enzyme replacement therapy. With the mucus blocking the ducts of the pancreas, many individuals with CF are determined to be pancreatic insufficient, and must rely on replacement therapy

to assist with the absorption of nutrients and digestion of food. This requires many pills, multiple times per day. At a very young age, children with CF learn to swallow multiple pills, as it is a necessary and frequent part of their daily regimen.

CFTR modulator therapies are CFTR mutation specific. CFTR "potentiators" successfully assist the "gates" of the CFTR protein to stay open so as to allow more chloride ions to move into and out of the cells and improve the balance of salt and water, while CFTR "correctors" improve delivery of CFTR molecules to the cell membrane. Over 60% of respondents had a mutation that enables them to utilize Kalydeco®, Orkambi® or Symdeko®.

What is significant to note is the large number of interventions that must be performed on a daily basis, requiring significant amounts of time. The burden of care for cystic fibrosis is substantial.

> *You would probably never guess that I have only 31% lung function, and I take over 30 pills, do countless insulin shots for CF-related diabetes, and spend roughly four hours a day on breathing treatments and airway clearance just to stay alive. Daily medications range everything from bronchodilators, inhaled oral antibiotic, mucociliary clearance, and digestive enzymes, to things like short and long-acting insulin, vitamins, and the list goes on. When I'm sick, I go into the hospital for week-long courses of IV antibiotics. There are no breaks; no days off.*
>
> *— Emily K-G, 33 years old*

> *A typical day for me consists of hours of breathing treatments, airway clearance, exercise, handfuls of pills, sterilizing neb cups, and a healthy diet and this is all just the regular maintenance for when I am healthy. I work so hard day in and day out just to be able to breathe.*
>
> *— Somer, 39 years old*

> *Luke arose at 6:00 am this morning to commence his treatments. It starts with 15 minutes of hypertonic saline followed by 10 minutes of Pulmozyme, followed by 30 minutes of chest percussions, followed by nasal sinus rinses, followed by 2 sprays of Flonase, followed by 2 sprays of Astelin, followed by 4 puffs of Advair, followed by 20 mg of Prevacid, followed by 30,000 units of Creon, followed by 1.25 capfuls of Miralax mixed with water, followed by 2 pills of Orkambi, followed by 1 pill of Prozac, followed by 300 mg of Ursodiol, followed by 40 mg of Straterra, followed by 20 mg of Zyrtec, followed by 1 probiotic, which is followed by vitamin gel capsule. The time is now 7:30 in the morning.*
>
> *— Joey, father to Luke, 11 years old with CF*

Participants were then asked, ***"In considering the financial costs and time requirements related to the above therapies (listed in the polling results above), in general, how much do these medical devices/equipment, medicines, and/or counseling improve your/your affected family member's quality of life?"***

The responses were as follows:

Response	Number	Percent
In general, they have helped a great deal to manage the most difficult symptoms and to improve my/my family member's quality of life.	65	66%
In general, they have helped somewhat in managing the most difficult symptoms and to improve my/my family member's quality of life.	30	31%
In general, they have not helped much at all in managing the most difficult symptoms and to improve my/my family member's quality of life.	3	3%

98 Responses

The significance of these responses is difficult to ascertain, based on the varying ages of those living with CF who participated in the poll. Some respondents with CF were born prior to Pulmozyme, enteric-coated enzymes, inhaled antibiotics, mechanical vests for respiratory therapy, CFTR modulators, hypertonic saline, etc. These have all significantly impacted survival and quality of life for those with cystic fibrosis.

It is still important to note that approximately 30% of the combined respondents feel that the large time and financial requirements related to the therapies have only helped "somewhat" in managing the most difficult symptoms. As was repeated consistently throughout the day, even those able to benefit from the CFTR modulator drugs continue to have health complications, and no reduction in their burden of care. And for those with rare or nonsense mutations, in recent years there have been no new significant therapies developed to slow disease progression.

Side Effects of Therapies

Several meeting participants discussed the pain and negative outcomes they have experienced due to side effects of their medications. Medical management can be quite complex due to the multi-systemic impact of the disease, and the numerous medications that CF patients take daily. These may include antibiotics (inhaled, oral and IV), anti-fungal medication, GI therapies, insulin, pancreatic replacement enzymes, CFTR modulator therapies, liver disease medications, immunosuppressant and anti-rejection medications post-transplant, and medications to address symptoms of depression and anxiety. Treatment of one aspect of CF disease may lead to worsening of another condition. For example, the use of prednisone is common to address inflammation in the lungs and sinuses, yet prednisone causes blood sugars to rise dramatically making the management of CF-related diabetes very challenging.

> *I think one thing we would like to see is some appetite stimulants that are more effective and with less undesirable side effects… These medications can affect these children's liver and also, for her, it slowed down her digestion so much that she was unable to tolerate her feedings and she had so much vomiting that lasted far beyond the treatment with the medication.*
> *— Melissa, mother to Ava Claire, 7 years old with CF*

While antibiotics are critically important in treating exacerbations, many participants discussed the challenges they experience during the infusion of IV antibiotics. Several people shared that they have developed allergies. Others named a variety of complications triggered by IV antibiotics.

> *I have antibiotic drug-induced pancreatitis...It's excruciatingly painful, and it lasts for days.*
> *— Toni, 59 years old*

> *To be frank, it's debilitating. I am not actively engaged or enjoying life when I'm on IV antibiotics. The few that I can take, I have severe side effects from, so ... even after I stop the IV antibiotics, the side effects last far longer...I sometimes get hemolytic anemia, where my blood counts drop. Often my white blood cell count drops; nausea, fatigue, arthritis, fevers... every time I start IV antibiotics I spike a fever higher than 102. Chills. Muscle aches, body aches, headaches. And zero appetite, so I often lose a ton of weight as well.*
> *— Melanie, 38 years old*

Goals for Potential Treatments

Individuals with CF and their family members have numerous components to the daily medical regimen, and the time required is – for many – equal to or greater than a part-time job. Despite this, most individuals with cystic fibrosis continue to lose lung function while living with gastrointestinal issues, chronic cough, fatigue, diabetes, and other complications. When asked, ***"What would be the most important impacts from a new treatment for you or your affected family member? (Pick your top 4),"*** the responses were ranked as follows.

Impacts	Percent	Rank
Fewer lung infections/exacerbations	75%	1
Improved ability to breathe	73%	2
Improved GI/digestive issues	43%	3
Reduced fatigue	35%	4
More time to pursue non-CF related activities	34%	5
Relief from depression/anxiety	26%	6
Reduced social isolation	17%	7
Reduced sinus pain	14%	8
Reduced cancer risk post-transplant	13%	9
Improved weight (BMI)	13%	9
Reduced side effects from post-transplant immunosuppressants	13%	9
Less pain	10%	10
Other*	7%	11

103 Responses

*Other: Therapies for rare mutations; reduced cough; reduced need to inject insulin

Universally, respondents' primary goal for new therapies would be one that led to fewer lung infections and exacerbations, which lead to permanent lung function loss, pneumothorax, hemoptysis, long hospitalizations, IV antibiotics, lost work and school time, etc. This was followed closely by the goal of facilitating the improved ability to breathe.

> *I also suffer from chronic hemoptysis and, like Gunnar, I also culture mainly multiple drug resistant Pseudomonas aeruginosa. I am also, full disclosure, a clinical trial avid subject. I do many clinical trials, of which I'm in one now. I would love, love, love to see more antibiotics, specifically targeted at Pseudomonas. Earlier this year I was on IV antibiotics for 12 weeks because none of the medication combinations were working.*
>
> *— Melanie, 38 years old*

> *Every patient dreams of the day that we wake up and can take an unhindered, deep breath. In fact, when my peers ask me what it is like to have CF, I want so badly to ask them what it is like to take an unobstructed breath.*
>
> *— Lise Courtney, 24 years old*

> *We need things like an antibiotic that is localized to the lungs only… We need more medications for inflammation and overall more medications that do not have harmful side effects where we trade one problem for another.*
>
> *— Jen, mother to Michael, 16 with CF*

New therapies to improve GI/digestive symptoms ranked third as a target area for drug development. In light of the large number of participants who shared their experiences with chronic, and often debilitating, gastrointestinal issues, patients are eager for new therapies.

> *I pray for new medical trials that result in treatments that aid my complicated digestive issues...*
>
> *- Lise Courtney, 24 years old*

Respondents to the poll ranked "more time to pursue non CF-related activities" fourth. A consistent theme of the meeting was the extraordinary amount of daily time required by CF patients to follow their health regimen, keeping them from participating in other life activities. New therapies that do not require additional time would be highly valued as having a significant impact upon quality of life.

> *We would really like to see focus coming from the industry and the FDA on driving down the burden of these treatments, so maybe instead of hours per day for Natalie we can get it down to 30 minutes or less per day…*
>
> *— Arek, father to Natalie, 4 years with CF*

> *For me personally, I would like to see a treatment that gives me back some of the time that I've spent trying to stay healthy.*
>
> *— Anna, 31 years old*

Drugs to provide "relief from depression and anxiety" were desired by approximately one-fourth of the respondents. Mental health issues (depression, anxiety, isolation, post-traumatic stress) were consistently mentioned by individuals with CF, as well as parents of children with CF. While there are many non-medical strategies to address depression and anxiety, it is increasingly recognized that medical interventions may be necessary. Some CF centers have a psychiatrist embedded in the care team. Individuals can react to anti-depressants in highly variable ways; the development of new options that minimize drug interactions would be beneficial to those impacted by CF.

Anti-rejection drugs are critically important for those who have received a double lung transplant, but are well known for their side effects including kidney toxicity, hypertension, high blood sugars, GI complications. The necessary immunosuppression also leads to an extreme increase in cancer risk.

> *I wish there were better drugs for transplanted CF patients, specifically drugs for chronic rejection or bronchiolitis obliterans syndrome (BOS). This is a deadly disease that can spiral very quickly into lung failure; there is not treatment at all… Please remember that transplanted CF patients are the orphans of this orphan disease. We need new drugs to reduce the risks of cancer and infection, and to treat chronic rejection or BOS.*
>
> *— Isa, 46 years old*

As was compellingly shared by two panelists, there is an urgent need for focused drug development efforts to find new therapies for those with rare and nonsense mutations. This population is unable to benefit from the latest CFTR modulator drugs, and individuals live with the knowledge that they have few resources to slow respiratory decline.

> *Unfortunately, with two copies of a rare form of CF caused by a nonsense mutation, I am here to put a face to the outlying 10% that won't benefit from any of these (CFTR modulator) breakthroughs… there are 7,000 of us still waiting, for whom this disease remains the same killer that it was before 2012.*
>
> *— Emily K-G, 33 years old*

> *My best friend is a fellow CF patient who lives in California. She lives with a nonsense mutation, which means there are zero drugs on the market for her specific mutation or class of mutations. While I celebrate my success on Symdeko®, I cannot forget that despite the fact that we suffer from the same disease, my best friend's life looks very different than mine. She does not have the optimism of Symdeko®, in fact she does not even have the hope for her future knowing that there are successful drug trials in the pipeline that will benefit her. Instead, she is just waiting.*
>
> *— Lise Courtney, 24 years old*

> *…We would also like to see some novel medication come about for those mutations where the things that have come about over the last few years simply do not help.*
>
> *— Arek, father to Natalie, 4 years with CF*

Other goals for new therapies included hope that marijuana-derived products would be de-stigmatized so as to study their application with the CF community. One participant emailed about the positive impacts of marijuana-derived products as an appetite stimulant, while another shared the impact of medical marijuana in helping her son cope with anxiety and trauma related to medical procedures.

> *He was diagnosed with PTSD (post-traumatic stress disorder) and became a medical marijuana patient two years ago. He uses this for severe GI pain and anxiety relief before surgeries. It's been the only thing that works for times like this. I don't get how doctors are comfortable prescribing Percocet and morphine for his pain and nobody offers information about the much less addictive marijuana. It should be looked at for certain circumstances without the stigma that it currently has.*
>
> *— Megan, mother to Aidan, 14 years old with CF*

Drug Development Issues – Clinical Trials

The cystic fibrosis therapeutic pipeline is robust, and there are numerous clinical trials taking place at any given time. In light of the exclusions that are a necessary aspect of any clinical trial, including the wide range of CFTR mutations, age, lung function, other current therapies, pathogens in the lungs, BMI, other comorbidities, etc., the participation of many is required to advance drug studies.

Anecdotally, the cystic fibrosis community is known for its enthusiastic participation in clinical trials. This perception was confirmed by those participating in the Externally-Led Patient Focused Drug Development Meeting on Cystic Fibrosis. Repeatedly, participants expressed their desire to participate in clinical trials and their strong hope that the FDA and drug development companies would create new definitions for clinical trial outcomes, so as to expand eligibility for participation.

In a poll, meeting participants were asked, ***"What is your experience with, and perception of, clinical trials for a new drug to treat cystic fibrosis?"***

The responses were as follows:

Response Option	Number	Percent
I am currently participating in a trial	10	10%
I have participated in a trial, and I would do so again	49	49%
I have participated in a trial and I would not do so again	0	0%
I have not participated in a trial because I did not know about the opportunity	9	9%
I have not participated in a trial because I was not eligible	26	26%
I have not participated in a trial, although I was aware of the opportunity and eligible	3	3%
I would never participate in a clinical trial	0	0%
Not sure	3	3%

100 Responses

Of those responding to the poll on the day of the meeting, 75% were either participating currently, or had participated in the past and would do so again. Another 23% had not participated due to eligibility. Responses were slightly different with the respondents post meeting, of which nearly 50% were currently participating in a clinical trial, or had done so in the past. A slightly higher percentage was ineligible (28%), while 13% did not know about opportunities to participate. Only 5% would not participate despite eligibility, and 5% were not sure.

A follow up question asked: ***"If you have participated in a clinical trial but would not do so again, what are your reasons?"*** Of the 60 respondents, only 2 indicated they would not participate in a trial again, citing fear of receiving a placebo, excessive distance from trial site, missing work or school, and multiple clinic visits.

In a final question related to clinical trials, participants were asked:
"What would discourage you from participating in a clinical trial for a potential new cystic fibrosis therapy?"

Response Option	Percent	Rank
None of the above	38%	1
Excessive distance from clinic	32%	2
Missing work/school	29%	3
Multiple clinic visits	18%	4
Potential placebo	14%	5
Blood draws	7%	6

101 Responses

Responses demonstrate a strong commitment to participation in clinical trials, with nearly half indicating that distance, placebo, blood draws, missed work, and multiple clinic visits would not discourage their participation.

A universal theme in discussing drug development clinical trials was a commitment to participation. Many attendees shared the pain they feel watching their friends and peers die from complications of cystic fibrosis. A common sentiment was the desire to participate in clinical trials not only for personal health, but with the hope that others might benefit in the future. There is a culture and awareness of "passing it forward," to others who may benefit in the future.

> *I actually participated in the clinical trial for that drug (Orkambi®) for over a year. It required 4:00 am blood draws almost weekly for the last few months. I wanted to make sure the trial didn't interfere with my job so I would get up super early, as the trial required an extra hour of driving. At no point did I think about giving up on the trial because I know that this medication could help keep my friends alive longer. I had to use my vacation time from work for some of the appointments, but I didn't care. To me, if these medications got approved then there would be more time for vacations later.*
>
> *— Anna, 31 years old*

> *I finally got to participate in the trial for Symdeko®, which did feel like the lottery. What I did not realize until the day I started was how vulnerable I felt. I was so focused on being able to try something that I did not think about the possibility of a negative outcome. That being said, I would do it again in a heartbeat. The drug has not improved my FEV1 as I'd hoped, but it has helped so many.*
>
> *— Melissa, adult with CF*

Assumption of Risk

Numerous meeting participants expressed their willingness to assume risks while taking part in clinical trials. The severely debilitating impacts of the disease continue despite a diverse range of therapies. Pain and inconvenience did not serve as deterrents to clinical trial participation.

> *We are willing to accept risk, not because of some kind of "therapeutic misconception," but because as highly educated and informed patients, we can be more objective than investigators. We can more readily accept many potential adverse outcomes of new therapies, rather than accept the inevitable natural course of his disease.*
>
> *— Laura, mother to 22-year-old son with CF*

> *We are willing to take on risks. We understand what they are. We have amazing doctors and an amazing team that works with us. We are willing to learn what the risks are and take on those on those risks. We know things can go sideways; we're okay with that. We'll take these*

calculated risks so that she may have a future and some potential.
— Arek, father to Natalie, 4 Years old with CF

I wanted to talk about was our eagerness to be involved in clinical trials. My daughter has a rare mutation, and she was left out of so many trials over the years. We were able to find an End-of-Line study where they harvested her nasal cells and shipped them across the country and grew them in a laboratory with the hopes of exposing them to a modulator drug… Despite how painful the procedure was for her to harvest these nasal cells, we wanted to push through and do it again. She had her cells harvested again, we shipped them across the country; they grew the cells, they grew beautifully. They were exposed to the drugs and they proved to not benefit from the drugs. But we're so grateful for the opportunity, and are looking for more opportunities to participate in clinical trials, even if they are inconvenient or if they're painful. We are eager and available.
— Melissa, mother to Ava Claire, 7 years old with CF

I have been fortunate enough to participate in many clinical trials throughout my life… I live an hour and a half from my CF clinic so I spend 3 hours traveling to and from the trials, and then the trials themselves often involve hours of sitting around at the hospital. But when you talk to me or any other CF patient about what it is like to participate in a clinical trial, it is like we have won the lottery. Yes, clinical trials require the patient to spend more time at the doctor and to devote extra time to treatments, but that all does not matter when we consider the possibility that this could make life with CF more bearable.
— Lise Courtney, 24 years old

Consistently, participants voiced their strong desire to participate, with hopes that criteria for participation would be expanded beyond the current norms – most often referring to exclusions based on FEV1.

When balancing risk and benefit, it is important not to underestimate the severity and suffering that results from this relentless disease and to understand that lung function does not paint the whole picture.
— Laura, mother to 22-year-old son with CF

But for many years I've had low lung function which is considered advanced lung disease, and I've been excluded (from clinical trials)… We all want to be a part of the trials, and I just think that I want drug companies and the FDA to analyze whether this one variable should be a deciding factor… I think that other metrics could be used besides FEV1 for this group, such as patient reported outcomes, or reduction of exacerbation frequency. And these measurements could be used for applying for FDA approval, and is something that I think that the FDA and drug companies can work together to understand these other metrics and illustrating this kind of data for providing approval, especially in a category of patients with this lower lung function.
— Ella, 26 years old

For those with rare mutations, the urgent need for new drug development strategies was passionately expressed.

FDA, we need your ingenuity and partnership to develop new paradigms that can speed race the breakthroughs of tomorrow. For patients with untreatable mutations and particularly those with advanced stage disease, the status quo is fraught with danger. We need you to prioritize drug reviews for people who are waiting, making a difference between life and death. Buying time is critical and stability is a win. Even drugs with a potential for risk in the future are bets we're willing to take for time we'd otherwise never have.
— Emily K-G, 33 years old

Please consider N-of-1 studies as a valid option for a clinical trial. I don't see any other way that people with rare mutations will gain access to these groundbreaking treatments.
– Jeannine, adult with CF

Incorporating Patient Input into a Benefit-Risk Assessment Framework for Cystic Fibrosis

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and caregivers through the CF Patient-Focused Drug Development meeting and written comments will inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the sample framework for CF, below, draws from various sources, including what was discussed at the CF Patient-Focused Drug Development meeting held on October 29, 2018. This sample framework contains the kind of information that, it is anticipated, could be included in a framework completed for a medical product under review for CF. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	–- Cystic fibrosis (CF) is a complex, capricious, multi-systemic, and debilitating disease. The autosomal recessive genetic disorder is caused by mutations in a gene on the seventh chromosome that makes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Only 30,000 people in the United States have been diagnosed with cystic fibrosis. One must have two copies of the mutated gene to have the disease. –- Since the implementation of newborn screening in every state, disease is now diagnosed in the majority of patients by age 2. However, many older children and adults receive a late diagnosis. – CF negatively impacts every organ system. Exacerbations (lung infections), hemoptysis (lung bleeds) and pneumothorax (lung collapse) are common, as are CF-related diabetes, sinus polyps, pancreatic insufficiency, gastrointestinal blockages, pancreatitis, liver disease, malnutrition, osteoporosis, and reproductive health challenges. – The symptoms of CF can vary widely from person to person, based on factors such as genetic mutation, age of diagnosis, environmental exposures, and other health issues. –- Respiratory complications are the primary challenge and source of concern for patients. However, mental health issues and gastrointestinal complications also significantly impact CF patients' quality of life. – CF negatively impacts people's ability to spend time with friends and participate in social activities, as well as their attendance at work and/or school. Those living with CF worry deeply about advancing lung disease and death, and well as their ability to maintain financial stability and live independently. –- The median age of death for those with CF is 30, with most deaths caused by respiratory failure.	Cystic fibrosis (CF) is a serious, progressive, debilitating and eventually fatal disease. CF is multisystemic, with different patients having different spectrums of disease. Respiratory symptoms – lung infections, bleeds, and collapse – and declining pulmonary function are the hallmark of CF. However, gastrointestinal issues and mental health are pervasive. Patients fear advancing lung disease and death, as well as loss of independence over time.
Current Treatment Options	– Therapies for cystic fibrosis create a significant daily burden of care, with patients spending between 2 and 5 hours per day following their medical regimen, with hopes only of slowing disease progression. – Therapies include airway clearance, multiple nebulized medications (bronchodilators, hypertonic saline, DNase, antibiotics), pancreatic enzyme replacement, insulin, oral antibiotics, vitamins, IV antibiotics, enteral feedings, and mental health interventions. – New CFTR modulator drugs have helped improve lung function for some, but they are not a cure, and are not effective for all CFTR mutations. – Side effects of medications often worsen CF patients' health. Many of the drugs can damage the liver; some IV antibiotics lead to permanent deafness or trigger dangerous allergic responses; post-transplant immunosuppressants increase the risk of cancer and are nephrotoxic; steroids used to reduce inflammation exacerbate CF-related diabetes; increasingly pathogens develop resistance to available antibiotics. – Individuals with CF who have received double lung transplants still must cope with the impacts of CF, along with an often-debilitating regimen of immunosuppressants to hold off organ rejection.	While new therapies have increased the life expectancy for those with CF, there is still no cure, and not all CF patients are amendable to currently-approved drugs. Patients express a great desire for treatments that would be able to reduce exacerbations – serious lung infections which lead to permanent lung function loss, pneumothorax, hemoptysis, hospitalizations, IV antibiotics, and lost work/school time. Therapies that improve patients' ability to breathe or address gastrointestinal complications would be of great value. In light of the current treatment burden, new therapies that do not require additional time would be highly valued.

Conclusion and Summary

CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis provided a meaningful opportunity for individuals with CF to share their experiences with those who are in the position to assess therapies that impact their lives. Diagnosed in only 30,000 people in the United States, CF is a rare disease. There have been many advances in CF therapies in recent decades, with an accompanying increase in life expectancy. But these therapies are not cures, and they are slowing disease progression at best. Many individuals with CF shared the high levels of anxiety and depression they live with. Many have lost friends to the disease, and have a very acute sense of their own mortality. Last year, half of those who died due to CF complications were under the age of 30, and the pain and suffering of those living with the disease is substantial.

Cystic fibrosis is a complex multi-systemic disease, and as was shared with brutal honesty, it negatively impacts every organ system. Lung infections, lung bleeds and lung collapse are common, as are CF related diabetes, sinus polyps, liver disease, osteoporosis, reproductive health challenges, mental health issues, and nutritional complications.

The growing arsenal of therapies has improved longevity and, for many, quality of life. But the burden of care is massive, and as was compellingly shared via this meeting, the treatment regimen requires hours every day, with no reprieve. Many of these therapies have side effects, and as was made clear at the meeting, because of the multi-systemic nature of the disease, these side effects often have a negative domino effect upon the body. Increasingly, antibiotic resistance develops in the pathogens colonizing CF patients' lungs, and many experience acute anxiety as their treatment options steadily shrink.

The cystic fibrosis community is committed to participation in clinical trials. It was clear that the motivation to do so goes beyond one's own survival – the rewarding knowledge that participation would help others was consistently expressed. Those who spoke shared that getting into certain trials was like "winning the lottery." Others expressed the desire for revised criteria for clinical trials that would incorporate more factors than FEV1.

Cystic fibrosis research and drug development is further complicated due to the variation in CFTR mutations. For those with rare mutations there are few new therapeutic options. One woman with a rare mutation referred to herself and her peers as the "orphans of the orphan disease." The desire for enhanced research, drug development and trials for this population was passionately expressed.

Individuals with CF who have received double lung transplants still must cope with the impacts of cystic fibrosis, along with an often debilitating regimen of immunosuppressants to hold off organ rejection. These drugs cause other potentially life threatening issues, including significantly higher rates of infection and cancer.

It is the hope of those living with CF that the Patient-Focused Drug Development Meeting on Cystic Fibrosis was only the beginning of an ongoing conversation, and that lines of communication remain open between the FDA and the cystic fibrosis community. We want to continue to share our experiences and serve as a resource to those who are assessing the value and efficacy of CF-related therapies.

It is our sincere hope that those who are reviewing drugs in the pipeline make cystic fibrosis a priority. For those with CF, every day really does matter. The cataclysmic fall to transplant or death is far too common for members of our community. Many members of our community have mutations that are not responsive to the CFTR modulating drugs. Too many people are still suffering and dying. The cystic fibrosis community is strong and resilient in the face of great hardship and tragedy, and is unfailing in its commitment to assume risks and participate in clinical trials so as to advance drug development.

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Appendix 1: Meeting Agenda

Patient-Focused Drug Development Meeting on Cystic Fibrosis Schedule

9:15 AM – 9:45 AM	**Registration & Continental Breakfast**
9:45 AM – 9:55 AM	**Welcome** Siri Vaeth, MSW, **Executive Director**, Cystic Fibrosis Research, Inc.
9:55 AM – 10:10 AM	**Opening Remarks** Boomer Esiason – Taped Welcoming Comments Robert Lim, MD, Lead Medical Officer Div. of Pulmonary, Allergy, and Rheumatology Products (DPARP) Center for Drug Evaluation and Research, F.D.A.
10:10 AM – 10:25 AM	**Background on Cystic Fibrosis** Ahmet Uluer, DO, MPH, CF Pulmonologist Boston Children's Hospital/Harvard
10:25 AM – 10:35 AM	**Goals and Objectives for the Meeting and Overview of Discussion Format** James Valentine, JD, MHS, Moderator
10:35 AM – 10:45 AM	**Demographic Polling** James Valentine, JD, MHS, Moderator

Topic #1: Disease Symptoms and Daily Impacts that Matter Most to Adults & Children with Cystic Fibrosis

10:45 AM – 11:05 AM	**Pediatric Caregiver Perspectives on Topic 1** A panel of four parents of children/adolescents with cystic fibrosis will provide comments to questions from the moderator. Kat Quinn Porco, MS; Jen Caruso; Joey Klausing, JD; Jane Mitchell. [Participation in person]
11:10 AM – 11:30 AM	**Adult Perspectives on Topic 1** A panel of four adults with cystic fibrosis will provide comments to questions from moderator. Emily Kramer-Golinkoff, MBE; Gunnar Esiason; Lise Courtney D'Amico; Emily Schaller, [Participation in person and remotely]
11:30 AM – 11:40 AM	**Pediatric and Adult Experience Polling**
11:40 AM – 11:45 AM	**Stand and Stretch**
11:45 AM – 12:30 PM	**Large-Group Facilitated Discussion on Topic 1** James Valentine, JD, MHS, Moderator *Individuals with cystic fibrosis and caregivers of adults in the audience are invited to participate in the dialogue.*
12:30 PM – 1:10 PM	**Lunch Break (Boxed Lunches)**

Afternoon Session

Topic #2: Perspectives on Current Approaches to Treating CF; Goals for Potential Treatments; Drug Development Issues: Individuals with Cystic Fibrosis and their Caregivers

1:10 PM – 1:30 PM	**Pediatric Caregiver Perspectives on Topic 2** A panel of four parents of children/adolescents with cystic fibrosis will provide comments. Kat Quinn Porco, MS; Jen Caruso; Joey Klausing, JD; Arek Puzia, MBA, CPA [Participation in person]
1:35 PM – 1:55 PM	**Adult Perspectives on Topic 2** A panel of four adults with cystic fibrosis will provide comments to questions from moderator. Emily Kramer-Golinkoff, MBE; Lise Courtney D'Amico; Anna Payne; Isa Stenzel-Byrnes, LCSW, MPH [Participation in person and remotely]
1:55 PM – 2:05 PM	**Pediatric and Adult Perspectives on Topic 2 - Polling**
2:05 PM – 2:45 PM	**Large-Group Facilitated Discussion on Topic 2** James Valentine, JD, MHS, Moderator *Individuals with cystic fibrosis and caregivers in the audience are invited to participate in the dialogue*
2:45 PM – 2:50 PM	**Stand and Stretch**
2:50 PM – 3:05 PM	**Closing Remarks:** Tejashri Purohit-Sheth, MD Director, Div. of Clinical Evaluation and Pharmacology/Toxicology Office of Tissue and Advanced Therapies Center for Biologics Evaluation and Research, F.D.A
3:05 PM – 3:15 PM	**Next Steps** Siri Vaeth, Cystic Fibrosis Research, Inc.

Appendix 2: Sponsors

CFRI's Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis is Generously Sponsored By:

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Appendix 3: Meeting Discussion Questions

Cystic Fibrosis – Issues for Discussion

Topic 1: Disease symptoms and daily impacts that matter most to patients with cystic fibrosis or their parents

1) Of all the symptoms that you or your child experience because of CF, which 1 - 4 symptoms have the most significant impact on your life or your child's life?

2) Are there specific activities that are important to you or your child but that you or your child cannot do at all or as fully as you would like because of CF? (Examples of activities may include missing life events due to illness; lacking time to participate in life activities due to extensive time required for medical regimen adherence; difficulty walking/running/participating in active events; missing life events due to mental health issues related to having CF; unable to spend time with others with CF due to cross infection risks.)

3) How do your symptoms affect you or your child's daily life on the best days? On the worst days?

4) How has your or your child's ability to cope with these symptoms changed over time?

5) Do your or your child's CF-related issues change? Have you or your child experienced a steady health decline or have you or your child experienced a cycle of decline and improvement? If so, do you know of anything that makes your or your child's symptoms better? Worse?

6) What frustrates you most about your condition or your child's condition?

7) What worries your child or you the most about your/your child's condition?

8) What do you fear for your or your child's future? What does your child fear?

9) What are your or your child's hopes for the future?

Topic 2: Perspectives on current approaches to treating cystic fibrosis and goals for potential treatments from individuals with CF and/or their parents

1) What are you or your child currently doing to help treat CF or its symptoms? (Examples may include prescription medicines, over-the-counter products, IV antibiotics, and adjunctive therapies such as exercise, acupuncture, massage, vitamins, and yoga.)

2) What specific symptoms do your or your child's treatments address?

3) How well does your or your child's current treatment regimen treat the most significant symptoms of cystic fibrosis?

Topic 2 Continued: Perspectives on current approaches to treating cystic fibrosis and goals for potential treatments from individuals with CF and/or their parents

4) How well do these treatments improve the ability to do specific activities that are important to you or your child's daily life? What activities are you or your child still unable to do?

5) What are the most significant downsides to current treatments, and how do they affect your or your child's daily life? What about these treatments make adherence difficult?

6) What specific things would you look for in an ideal treatment for your or your child's cystic fibrosis? What issues would you most like a potential treatment to address?

7) It is believed that numerous drugs in the CF therapeutic pipeline may eventually halt the progression of the disease among 90% of the population. What impact does this knowledge have upon your or your child's mental wellbeing? What life changes do you anticipate should any of these therapies come to fruition?

8) Have you or your child ever participated in a clinical trial? What was your experience? Is there anything you wish you had known prior to your or your child's participation in the clinical trial?

9) Would you or your child participate in a clinical trial that did not include a placebo (i.e. you or your child are definitely receiving the drug).

10) How important is it for biopharmaceutical companies to explore new drug development for individuals who have received double lung transplants? Should this be a priority over drug development for those who have not yet received a double lung transplant?

Appendix 4: Polling Responses — Condensed

Externally-Led Patient-Focused Drug Development Meeting on Cystic Fibrosis Polling Questions/Responses

Date of Participation	Number of Participants (%)
10/29/2018	141 (69%)
After PFDD	61 (31%)

Where do you live?	Number of Participants (%)
Eastern Standard Time Zone	78 (55%)
Pacific Standard Time Zone	34 (24%)
Other (Mountain & Central Time Zones)	29 (21%)

Do you live in:	Number of Participants (%)
A city	62 (44.4%)
A rural area	53 (37.4%)
A suburban area	26 (18.2%)

Which of the following best describes you?	Number of Participants (%) Day of PFDD	Number of Participants (%) After PFDD
Individual with CF	27 (19%)	31 (52%)
Family member of person with CF	42 (30%)	28 (46%)
Representatives of medical equipment for biopharmaceutical companies	22 (16%)	
Other (CF clinicians, researchers, government employees, or advocacy group members	49 (35%)	

Gender of Participant	Number of Participants (%) Day of PFDD	Number of Participants (%) After PFDD
Male	30 (21%)	12 (21%)
Female	111 (79%)	49 (79%)

Distance Traveled to CF Center	Number of Participants (%) Day of PFDD	Number of Participants (%) After PFDD
Less than 25 miles	73 (52%)	28 (46%)
25 to 50 miles	21 (15%)	10 (18%)
More than 50 miles	46 (33%)	23 (36%)

Health insurance coverage	Number of Participants (%) Day of PFDD	Number of Participants (%) After PFDD
State Medicare/Medicaid	50 (36%)	15 (26%)
Family member's employment	46 (33%)	28 (46%)
Private Insurance	45 (31%)	17 (28%)

Which of the following CF-related symptoms do you or your loved on cope with on a regular basis?	Total Number of Participants (%) (103 Participants)	Rank
Gastrointestinal Issues	74%	1
Pulmonary Exacerbations/Infections	72%	2
Excessive Cough	65%	3
Sinus Disease	59%	4
Mental Health Issues	58%	5
Fatigue	58%	5
Shortness of Breath	57%	6
Tight Chest	38%	7
CF-Related Diabetes	33%	8
Chronic Pain	32%	9
Liver Disease	7%	10

How has the impact of your/your loved one's cystic fibrosis changed over time (home, school, work, friendships, intimate relationships, etc.)?	Total Number of Participants (%) (103 Participants)
Impact has gotten greater or affects additional areas of our life	77%
Impact remained the same	14%
Impact had lessened	7%

Which of the following CF-related symptoms most impact you quality of life?	Total Number of Participants (%) (102 Participants)	Rank
Pulmonary Exacerbations/Infections	69%	1
Excessive Cough	48%	2
Gastrointestinal Issues	47%	3
Fatigue	39%	4
Shortness of Breath	37%	5
Mental Health Issues	33%	6
Sinus Disease	32%	7
CF-Related Diabetes	21%	8
Chronic Pain	18%	9
Tight chest	10%	10
Liver Disease	1%	11

What are the most important things you or your family member with CF have found to be more challenging because of your/his/her diagnosis with cystic fibrosis?	Total Number of Participants (%) (100 Participants)	Rank
Spending time with friends/participation in social activities	67%	1
Attendance at work or school	54%	2
Participation in sports or extracurricular activities	56%	3
Maintaining financial stability	36%	4
Other	24%	5
Finding/Keeping a job	22%	6
Performing well at school or work	16%	7

What are the issues that worry you/your loved one most about life with cystic fibrosis?	Total Number of Participants (%) (100 Participants)	Rank
Advancing lung disease	81%	1
Death	44%	2
Social Isolation	35%	3
Transplant	34%	4
Mental/Emotional Health	32%	5
Ability to live independently	31%	6
Finding a job/career success	20%	7
Physical Pain	15%	8
Other	6%	9
Academic Success	4%	10

What are you/your child currently doing to help treat the condition or its impacts?	Total Number of Participants (%) (98 Participants)	Rank
Airway Clearance	90%	1
Inhaled/Nebulized Bronchodilators	84%	2
Nebulized Hypertonic Saline	82%	3
Pancreatic Enzyme Replacement	78%	4
Nebulized Dnase	69%	5
Inhaled Antibiotics	64%	6
Oral Antibiotics	62%	7
Mental Health Interventions	44%	8
CFTR Modulators	43%	9
IV Antibiotics	33%	10
Insulin	29%	11
Other (nutritional supplement, vitamins, anti-rejections medications post-transplant, antibiotics sinus flushes)	29%	11
Enteral Feedings (G-Tube)	11%	12
None	0%	13

How much do medical devices/equipment, medicines, and/or counseling improve you/your affected family member's quality of life?	Total Number of Participants (%) (98 Participants)	Rank
In general, they have helped a great deal to manage the most difficult symptoms and to improve my/my family member's quality of life.	66%	1
In general, they have helped somewhat in managing the most difficult symptoms and to improve my/my family member's quality of life.	30%	2
In general, they have not helped much at all in managing the most difficult symptoms and to improve my/my family member's quality of life.	4%	3

What would be the most important impacts from a new treatment for you or your affected family member?	Total Number of Participants (%) (103 Participants)	Rank
Fewer lung infections/exacerbations	73%	1
Improved ability to breathe	71%	2
Improved GI/digestive issues	42%	3
More time to pursue non-CF related activities	33%	4
Reduced fatigue	33%	4
Relief from depression/anxiety	24%	5
Reduced social isolation	14%	6
Reduced cancer risk post-transplant	13%	7
Reduced sinus pain	11%	8
Improved weight (BMI)	10%	9
Reduced side effects from post-transplant	10%	9
Less pain	10%	10
Other (Therapies for rare mutations, reduced cough, reduced need to inject insulin)	5%	11

What is your experience with, and perception of, clinical trials for a new drug to treat cystic fibrosis?	Total Number of Participants (%) (100 Participants)	Rank
I have participated in a trial, and I would do so again.	49%	1
I have not participated in trial because I was not eligible	26%	2
I am currently participating in a trial	10%	3
I have not participated in a trial because I did not know about the opportunity	9%	4
I have not participated in a trial, although I was aware of the opportunity and eligible	3%	5
Not sure	3%	5
I have participated in a trial and I would not do so again	0%	6
I would never participate in a clinical trial	0%	6

What would discourage you from participating in a clinical trial for a potential new cystic fibrosis therapy?	Total Number of Participants (%) (101 Participants)	Rank
None of these options	32%	1
Excessive distance from clinic	30%	2
Missing work/school	27%	3
Multiple clinic visits	18%	4
Potential placebo	12%	5
Blood draws	5%	6

Appendix 5: Speakers — Biographies

Boomer Esiason

Boomer Esiason enjoyed a 14-year NFL career as a quarterback for the Cincinnati Bengals, New York Jets and Arizona Cardinals. A four-time Pro Bowl quarterback, 1988 NFL MVP, and champion of many charitable causes, Esiason began focusing on cystic fibrosis in 1993 when his son, Gunnar, was diagnosed with the disease. In 1994, Esiason launched the Boomer Esiason Foundation (BEF), which joined medical and business communities with a committed core of volunteers to heighten awareness, education and quality of life for those affected by CF, while providing financial support to research aimed at finding a cure. Since its inception, the BEF has raised more than $140 million to support CF research and programs directly benefiting the CF community, including a recent movement to create state-of-the-art CF facilities while instituting educational, awareness and adherence programs for adults with CF. Esiason helps bring CF to policy discussions in Washington D.C. and throughout the U.S. Upon retiring from the NFL, Esiason was a popular commentator for ABC's NFL "Monday Night Football," and Westwood One Radio's "Monday Night Football." He is currently a co-host on CBS Sports' "The NFL Today," co-host of WFAN's national morning radio show, "Boomer and Gio," which is simulcast on the CBS Sports Television Network, and since 2015 co-hosts Showtime's "Inside the NFL." Esiason, and his wife, Cheryl, have two children, Gunnar and Sydney. They reside in Manhasset, NY.

Robert Lim, MD

Dr. Robert Lim is currently a clinical team leader in the Division of Pulmonary Allergy and Rheuma-tology Products (DPARP) in the Center for Drug Evaluation and Research at the Food and Drug Administration. He completed his pediatric residency at the University of Maryland Medical Center and pediatric pulmonology fellowship at Boston Children's Hospital. Following fellowship, he was an attending physician at Boston Children's Hospital and was involved in the care of cystic fibrosis patients. He joined the FDA in 2011 as a medical officer in DPARP and became a clinical team leader in 2017. While at the FDA, he has been involved in the review of multiple products aimed at treating patients with cystic fibrosis.

Tejashri Purohit-Sheth, MD

Dr. Tejashri Purohit-Sheth is currently the Director of the Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT) in the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research at the Food and Drug Administration. She provides supervi-sory oversight for the clinical and pharmacology/toxicology review of submissions to OTAT. She previously served as the Clinical Deputy Director in DAGRID/ ODE/CDRH/FDA as well as Acting Division Director and Branch Chief in Office of Scientific Investigation in CDER/FDA and as a Medical Officer in the Division of Pulmonary and Allergy Products (CDER/FDA).

She completed an Internal Medicine Residency at Naval Medical Center Portsmouth followed by a fellowship in Allergy/Immunology at Walter Reed Army Medical Center. Following fellowship, she took over as Service Chief of the Allergy/Immunology clinic at National Naval Medical Center in Bethesda, MD. Following her end of obligated service as an active duty Naval Officer, she transferred her commission to the U.S. Public Health Service and began her FDA career; currently she has served for 24 years as an active duty Uniformed Service Officer.

Ahmet Uluer, DO, MPH

Ahmet Uluer is a medicine and pediatrics trained pulmonologist and Director of the Adult Cystic Fibrosis Program at the combined Boston Children's Hospital and Brigham & Women's Hospital Cystic Fibrosis Center. After graduating from the Kansas City University School of Medicine and Biosciences, he completed his Med-Peds Residency at the Cleveland Clinic where he also served as Chief Resident. He completed his pulmonary fellowship at Boston Children's Hospital and earned his Master's in Public Health at the Harvard TH Chan School of Public Health. He is Director of the Weitzman Family Bridges Adult Transition Program at Boston Children's Hospital, providing age-appropriate care and transitional care support to adult survivors of congenital or pediatric acquired chronic illness, and working on transitional care processes and outcome measures for those with childhood-onset chronic diseases. His clinical and research interests involve all aspects of cystic fibrosis care, including quality improvement initiatives, transitional care and outcomes research. He is very interested in complications related to current pulmonary therapies, including nephrotoxicity and ototoxicity.

James E. Valentine, JD, MHS / *Moderator*

James Valentine is an associate attorney at Hyman, Phelps & McNamara where he assists medical product industry and patient advocacy organiza-tion clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Mr. Valentine also works with clients on clinical trials operations and compliance matters. Before joining the firm in 2014, Mr. Valentine worked in the FDA's Office of Health and Constituent Affairs (previously Office of Special Health Issues) where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues. Mr. Valentine administered the FDA Patient Representative Program, facilitated stakeholder consultations during the reauthorization of PDUFA and MDUFA, helped launch the Patient-Focused Drug Development program, and developed the FDA Patient Network. Mr. Valentine also worked at the Center for Drug Evaluation and Research's (CDER) Office of Regulatory Policy where he coordinated the implementation of the medical gases certification scheme that was established in FDASIA and handled a variety of post-market safety issues including REMS and safety labeling changes.

Siri Vaeth, MSW / *CFRI Executive Director*

Siri Vaeth first became involved with CFRI soon after her daughter's diagnosis with CF in 1995. As a volunteer, she raised funds, chaired the Newsletter Committee, and served on the Board of Directors for 10 years. She joined the CFRI staff in December 2013, where she most recently served as Associate Director. Siri earned her BA in Politics at UC Santa Cruz, and her Master's in Social Welfare at UC Berkeley. She brings over 25 years of nonprofit experience to CFRI, including previous positions as executive director of Big Brothers Big Sisters of Santa Cruz County, contract grant writer for several nonprofit organizations, and social worker with the Head Start program.

Appendix 6: Panelist — Biographies

Jen Caruso

Jen Caruso is a working mother of a 15-year-old boy, Michael, who has cystic fibrosis. She is a wife, mother and step-mom to two other children. Jen manages three departments for a company in the pharmaceutical industry, including an Inside Sales team, Customer Service and Sales Operations departments. Despite a very busy work schedule with high demands, she has always dedicated herself to helping raise awareness and funds for CF. She is a passionate advocate for the disease and through the years has helped raised awareness for the CF Foundation in her local community. She goes to Washington yearly to continue to ensure the cystic fibrosis community has a voice in protecting our healthcare for those with rare diseases and preexisting conditions. Jen also spends time fundraising locally for CF walks, galas and other events throughout the year. Finding a cure for cystic fibrosis has become not only her mission but her family's as well. They believe that together we will see a cure in Michael's lifetime for all those with CF.

Lise Courtney D'Amico

Lise Courtney is 24 years old and was diagnosed with cystic fibrosis at the age of two after suffering from malabsorption. She grew up in the Washington D.C. metro area, and now resides in New York City. After graduating from high school, she attended Boston College, where she studied math and economics. She now works as a business consultant. Lise Courtney has been blessed with fairly stable health throughout her life, but is well aware of the increasing number of ways that CF is impacting her daily life. She strongly believes in exercise as a form of airway clearance, so when she is not at work you can usually find her at the gym trying to clear her lungs. She also enjoys attending Orioles and Capitals games. In addition, Lise Courtney is involved with the CF Foundation.

Gunnar Esiason

Gunnar is a successful 27-year-old young man living with cystic fibrosis. After graduating from Boston College in 2013, he is now a program director, patient advocate and board member at the Boomer Esiason Foundation, the charity his parents started upon learning of his cystic fibrosis diagnosis. Gunnar is also a co-host of Breathe In: A Cystic Fibrosis Podcast, a writer and the head coach of his high school alma mater's varsity ice hockey team. Above all else, Gunnar believes it is important for people living with chronic illness to feel empowered to advocate for themselves as equal individuals. He lives in New York.

Joey Klausing, JD

Joey Klausing is the Executive Director of Cure CF. Formed in 2015, Cure CF is an all-volunteer board, comprised of 14 individuals with various backgrounds, from healthcare to law to amateur athletics and beyond. Cure CF has raised and donated over $1,000,000 to local and national CF research projects. Joey graduated from Centre College with a Bachelor of Arts degree and from University of Louisville Brandeis School of Law, with his Juris Doctorate. Joey is happily married to his college sweetheart, Jessica. He enjoys spending time at home with his children, Luke age 11 who has CF and Emma who turns 7 today.

Emily Kramer-Golinkoff, MBE

Emily Kramer-Golinkoff is Co-Founder of Emily's Entourage, an innovative 501(c)3 foundation that accelerates research for new treatments and a cure for cystic fibrosis. She is also an internationally-recognized patient advocate and speaker.

Named a White House Precision Medicine "Champion of Change," Emily's Entourage has awarded over $3.4 million in research grants since 2011 and led worldwide efforts to drive high-impact research and drug development on nonsense mutations of cystic fibrosis. The organization has been featured in national media outlets, including CNN.com, Time.com, People.com, and AOL.com.

Emily has a Master's degree in bioethics and certification in Clinical Ethics Mediation from the University of Pennsylvania, where she also completed her undergraduate degree. She has given talks at The White House, TEDx, University of Pennsylvania's Annenberg School for Communication Commencement, Stan-ford University's Medicine X Conference, and more, and in 2016, she was the recipient of the Global Genes Rare Champion of Hope for Advocacy Award.

Jane Mitchell

Jane Mitchell is the mother of two children, Grayson and Hannah. Hannah is 7 years old, and was diagnosed with CF nine days after birth due to complications from meconium ileus. Jane has a BS in Business Management from Southern Oregon University. Prior to having children, she worked in the insurance industry. Jane's efforts are currently focused on her children, as well as CF advocacy, education and psychosocial support through CFRI. Jane serves on CFRI's Embrace Mothers Retreat Committee, as well as the National Education Conference Committee. Originally from Chicago, Jane and her husband Jonathan lived for years in the San Francisco Bay Area, until their move last year to Germantown, Tennessee.

Anna Payne

Anna Payne is a 31-year-old person with CF who is working on accomplishing her dreams every day. She recently got engaged, and moved into her dream condo with her fiancé and Geoffery (her beloved pet Pekingese). Her passion is helping raise awareness and support for cystic fibrosis. Every year her team, Anna's Bananas, raises money for the Cystic Fibrosis Foundation: this year she raised over $30,000 in honor of her 30th birthday! She works full time at the County of Bucks in Pennsylvania. Passionate about helping others, she works for a County Commissioner, where her job enables her to get involved in local politics and help people within the county. Anna is also a member of the Pennsylvania Rare Disease Advisory Council; she is one of only two patients on the Council. Her hope is that her life experiences will raise needed awareness about issues that patients with rare disease face daily. She does this while maintaining a strict regimen of treatments, pills, and taking care of herself, all while embracing life and realizing her passion for making a difference and helping others.

Kat Quinn Porco, MS

Kat holds a Bachelor's in Social Work, graduating cum laude, and her Master's of Science in Health Communications from Boston University. Her work over the past seven years has been solely focused on supporting and advocating for the cystic fibrosis community. Throughout these years, she has seen firsthand the disconnect between the recommendations of the medical community and subsequent applicability for the patient community. Understanding this complex relationship, Kat assists in bridging the gap to reach the ultimate health goals of both parties. Kat attended Duke Integrative Medicine to become a Duke

Certified Integrative Health Coach. In September 2017, Kat sat for the National Board Certification, through National Board of Medical Examiners and International Consortium for Health & Wellness Coaching. Kat is currently enrolled in the American Association of Diabetes Educators Level 2 Certificate program, to better support the CFRD community. Kat sits on the editorial board for CF Research News (a subsidiary of the CF Journal), is a member of advisory boards for both Gilead and Genentech and is a part of the Evidence Analysis Library Cystic Fibrosis Workgroup to develop the new nutrition guidelines for CF. She also contributes to the Mental Health Advisory Committee and Partnerships for Sustaining Daily Care through the CFF. with his children, Luke age 11 who has CF and Emma who turns 7 today.

Arek Puzia, MBA, CPA

Arek Puzia is the father of Natalie, a 4-year-old with cystic fibrosis. Arek, his wife, Marta, and Natalie live in Walnut Creek, California, and Natalie is their only child. Natalie is homozygous CFTRdele2,3(21kb), a class I mutation. Arek was originally born in Poland, but has lived in Califor-nia for most of his life. He has a Bachelor's degree in Business Economics from the University of California, Los Angeles, and a Master's in Business Administration from the University of Chicago Booth School of Business. After Natalie's diagnosis, Arek left a career on Wall Street to be better able to manage Natalie's cystic fibrosis treatment requirements along with Marta. He currently manages finances for working professionals and takes a strong interest in helping those with children who may require financial assis-tance their entire lives, as Natalie may need, to plan their financial future.

Emily Schaller

Emily Schaller, 36, is a heroine with one goal in mind, to Rock CF. Equal parts spark, wit and humor, Emily is claiming her victories against cystic fibrosis, having launched the Rock CF Foun-dation in 2007 to heighten public awareness and raise funds to increase the quality of life for everyone with CF. Emily created and manages an internationally acclaimed line of merchandise to help fulfill the mission of Rock CF. Today, Emily's battle against this deadly genetic disease is printed in Runner's World, FORBES, The Atlantic and SPIN magazines, the New York Times, The Washington Post, USA Today, NPR and posted on Competitor.com, Shape.com, the Associated Press, and various cystic fibrosis focused educational websites. She is a marathon runner, super teacher and a speaker, addressing parents, patients and audiences about the effects of cystic fibrosis and the ever-changing and improving treatments being made. Through Emily's humor and personal experience she inspires the masses to transform their lives with exercise, diet and goal setting.

Isabel Yuriko Stenzel Byrnes, LCSW, MPH

Isabel is a bereavement social worker at Mission Hospice, where she counsels and leads writing groups for those who are grieving. She has lived with cystic fibrosis (CF) for 46 years and received a double lung transplant fourteen years ago. Isabel has been an active leader for various CF and organ transplant organizations for over two decades. Isabel and her late twin published the memoir, "The Power of Two," and served as international patient advocates in their mother's country, Japan, which led to the creation of a documentary film of the same title. Isabel has lectured around the country on topics such as living well with illness, end-of-life issues and organ donation, including a TEDx Stanford talk in 2014. Isabel plays the bagpipes to celebrate her lung donor. She lives in Redwood City and is married to Andrew Byrnes.

Appendix 7: Panelists' Transcripts

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients with Cystic Fibrosis or Their Parents

Panel: Parents of Children with Cystic Fibrosis

Kat Porco, MS

My name is Kat Porco, I am the mother to two children. Maylie is 12, and is in constant battle against cystic fibrosis disease progression. Ellesse is 10, and also diagnosed with cystic fibrosis, just not genetically. Biology spared her with normal CFTR function, yet her life is utterly defined, shaped and torn apart by her sisters consuming disease.

Balance is a cruel pun not afforded to families who were awarded membership to the cystic fibrosis community. We try to maintain a version of normal, but that is virtually impossible. A much-anticipated day at the trampoline park, a distant cough is heard, all eyes on alert as we scan for the potential predator to our outpatient life. We see the child; the day is aborted. Nothing is worth the risk of our family being separated for yet another hospitalization. We slowly walk together toward the door, exuding disappointment, allowing the power that CF has over our lives to sink in. Our attempt to avoid admission number four this year is done at all costs, I have already missed seven weeks of Ellesse's life this year alone, thirty-nine weeks since Maylie's diagnosis. Now we will wait, hoping that we left soon enough.

Blood sugar levels slowly begin to rise, coughing increases, treatments begin to consume more than four hours a day. Ellesse's demeanor is supportive but apprehensive as she becomes increasingly aware of what lies ahead. Doctor appointments, teary eyes and Ellesse is quickly and quietly shipped to friends and family. Maylie's health dictates the course of the next few weeks, her physical needs above Ellesse's emotional needs. I allow my tears to speak to the weakness that lives within my heart, aching for my daughters. One in a constant, uphill battle for her life and the other watching quietly from the sidelines, observing the pain, running from the fury that she sees in her sister's eyes, relegated to the reality that she cannot fix the unfixable. Her best friend is racing against time. My tears, the only tangible evidence of the wounds inflicted upon my heart over their sisterly love and yet conflicting wars.

Ellesse lives a life dictated by cystic fibrosis. Her eyes, are a window to her soul. Searching for answers, slowly beginning to grasp the immensity of this disease. Her life consists of countless prodigious moments, but equally a darkness that she did not choose. She spends hours in waiting rooms, pharmacy lines and clinic appointments; her face showing the complex and unfair role of being a sibling to a sister living with a chronic, life-shortening disease. A role that she embraces without hesitation.

Watching from her supportive place on the treatment couch as her sister enters into a routine and predictable coughing spell, continuing until her face reddens and exhaustion takes over. She holds out her little hand in sympathy, a role I was not asked to perform until my 30s, yet at the young age of ten, she has mastered it with precision. Placing her fears in a box and offering her sister hope through her smile.

Holidays are often cut short by hospitalizations, family reunions go unattended, much anticipated play dates are cancelled due to a cough that threatens to propel us to yet another exacerbation. Home school, a reality that she accepted with complete grace and understanding, leaving behind friends without question, knowing the importance of protecting her big sister. This reality is haunting. Growing up facing the mortality of a sibling is consuming at times--and frightening all the time.

We strive to make our lives about all the moments in between what CF dictates, but the reality is that treatments, hospitalizations, appointments and blood draws fill our lives. Despite medical advances, our CF dedicated responsibilities demand more and more each year.

Rich blessings abound in countless areas of our life, but with that, there is always an underlying fear, a silent demon lurking in our house. A growing energy threatens to tear our family in half for days or weeks, whatever CF deems appropriate for the next hospitalization. Her strength through these hardships is truly a vision, she carries all the burdens with a beautiful sense of grace and understanding.

I envision what her life would have been like without the ugly face of CF invading it. Would she be happier or less

anxious without the constant sense of unease for her sister? What would their relationship be like without the burden of CF changing the dynamics of our family in an instant?

Thank you.

Jen Caruso

Hello My name is Jen Caruso, and I have a 15-year-old son with Cystic Fibrosis.

So let me tell you a little bit about my story and my son Michael's story. I remember the joys of being pregnant and knowing we were having a son. However, when he was born I just knew something was not right. Everyone told me I was crazy, "He's totally fine" they would say, he even weighed 9.1 pounds at birth. Call it mothers intuition, but I knew. They ended up diagnosing me with postpartum depression, my mother moved in for about a week to help me adjust all the while everyone was telling me, "Everything is ok, you are just a new mom who's scared."

Well, everything was not ok. We got phone call on Friday December 27th 2002 from our pediatrician office telling me that through the newborn screening they believed Michael had cystic fibrosis and I needed to see them Monday morning to discuss this further.

I remember this day like it was yesterday, I dropped the phone, ran outside the house, dropped to my knees and started to vomit. While I had a feeling something was not right, I never imagined it would be CF. I was praying every night that everyone else was right, and I was just a "scared new mom." I remember my parents coming over that night we got the phone call; no one knew what to say other than, "Maybe it's a mistake," and all I could do was cry as I thought back to my college days and my roommate's boyfriend, Bill Cook, who lost his battle to CF while we were in school. That's all I knew about the disease at the time - that it meant death at a very young age.

That following Monday we went to talk at the pediatrician's office and later would go for the sweat test to confirm the diagnosis. Michael, my sweet little baby, had cystic fibrosis.

I was completely heartbroken and scared. It was a few weeks later Michael had his 1st of many hospital admissions. When we left the hospital we went to the pharmacy to pick up his monthly supply of medications. I was in shock; the bag of medication was actually larger then my son. How was I supposed to put all this medication into him? How was my baby going to swallow medication? How would I keep it all straight: 14 different medications all with their own schedule, some every 6 hours, some every 8, some once a day, some twice a day, while others every time he ate. I had poster boards and sticky notes all other the house. We had to ask family to stay away if there was even the slightest change they were sick or even if they had a running nose.

When Michael was diagnosed, the median life expectancy for those with CF was in the early 30s. Keep in mind this was a median, we still have many kids dying from this disease and let's face it, 30, even 40 is still way too young.

Being Michael's mom has brought me the greatest joy in life; however, it comes with a big amount of worry and heartache. I am always worried every time he is sick, is this the one, is this the one that will knock him down or worse? Michael has spent every year in the hospital at least 3-6 times a year since birth, however it has now been 1 year and 9 months hospital free.

He has missed out on playing sports he wanted to play because he was too sick or too little. He still has regrets of never being able to play football. He was so skinny and with so many hospital stays it was just not something he could not do. Michael had a feeding tube from the age of 3 to 8 years old to help him with gaining weight. Every night during those years he would have to be hooked up to his feeding tube; those were long hard nights. The pump would go off multiple times a night because he got the hose kinked or something. He would ask me, "Why mom? Why do have to do this? I hate CF." Many times he could hear his friends outside playing, but he was just too sick to go so he would stare at the window. He would ask me "Why? Why do I have CF mom?" A question to this day I still cannot find the right words to answer.

As Michael gets older we are having to have much more difficult conversations about his future. Conversations that no parent should have to have with their child. Things from when he was young and 1st noticed that others did not have to take pills or be hooked up to a breathing machine. Try explaining to your young child that they are quote "special".

A couple of years ago it was around his life expectancy. My son generation is the generation of the internet… .man they use that for everything. He said "Mom, I'm going to die young if we don't find a cure, I read I will die before I am 35 and that's if I make it that long" Those conversations are gut wrenching. Lots of tears from both of us, but as we try to always control what we can, here and now. We get involved in advocacy and fundraising and it's helped us both with feeling more powerful in a very powerless situation.

My most recent conversation was just a few weeks ago. Now that we in the "fun" teenage years, he came to me and said, "Hey mom, can I have kids? I read 95% of CF males are sterile." Well I assured him someday he would be able to have kids, and how using thing like IVF would make that possible, however, that that day was not anytime soon since he still in high school (LOL).

Michael has hopes to go to college, get married, have kids, and live long into adulthood. With treatments on the horizon I believe all his dreams will come true. In the meantime, we advocate and fundraise for a cure to get us that much closer to making his dreams a reality.

Thank you.

Joey Klausing, JD

Good morning. I am Joey Klausing, executive director of Cure CF, a small non-profit in Louisville, KY. I am also a partner in a law firm, but my biggest job or responsibility is making sure my 11- year-old son with CF Luke outlives me!

In my hometown, on the 1st Saturday in May we have a little horserace called the KY Derby. I remember going out to handicap the horses and learn the odds 30 years ago during my childhood. Little did I know, in 2007, I would be playing the odds in in a different venue, the venue of CF.

During a prenatal screening, my wife called me in tears as she was found to be a carrier of the CF gene, which would be no big deal, unless I was a carrier too. I was. Even still we had a 75% chance of Luke not having CF. As my wife Jessica, a nurse, later told me, she knew he had CF the minute she kissed his forehead due to the salty taste.

The biggest challenges we have with Luke and cystic fibrosis stem from his mucus buildup and resultant infection. While the gastrointestinal side effects are there, specifically with pancreatic insufficiency and sludging of the liver, the thick, viscous mucous creates the most difficulties for us.

As a result of this symptom of cystic fibrosis, Luke does not attend sleepovers with his 6th grade classmates. Just recently Luke had a "sleep under" where we came and picked him up around 11:00, while the other classmates stayed and enjoyed the rest of the night. During flu season, or even if someone is merely coughing behind us at mass, we will take Luke to the church's narthex during the sign of peace in an effort to minimize his exposure to illness. When we travel on planes, Luke his forced to wear a mask. When we went overseas this past summer, we had an extra dose of an antibiotic with us just to be safe.

Yet, the summer months present just as much of a challenge due to his propensity to suffer from hyponatremic dehydration from sodium depletion. We often supplement his drinks with salt tablets in an effort to avoid fatigue and migraines. We struggle with finding the right balance between exercise and resultant airway clearance and making sure he is hemodynamically stable and maintaining his weight. We know a feeding tube may be in Luke's future, but we are trying to delay it as long as possible.

We are frustrated that we can't control the negative prognosis of Luke's life. In a warped way, we wish Luke would have had pediatric cancer, which has a 90% survival rate. Whereas his current survival rate is 0%. There are treatments and cures for cancer, and a person can become "cancer free." No one can become CF free.

Due to recent advances in the cystic fibrosis drug pipeline, many of which were only possible through the FDA's modification of its rules, Luke has had a positive past few years. As is typical with any CF parent, I need to knock on some wood right now so as not to jinx us!

Luke, a homozygous Delta f508 carrier, has been on Orkambi for the past 2 years and looks forward to starting on Symdeco or the triple therapy VX-669 when he turns 12 in April, or sooner if it becomes approved for ages 6-11. Prior to

Orkambi we had monthly visits with an ENT where she would insert a tube through his nose into his maxillary sinuses and then inject Gentamycin. We have only seen her once in 2 years!

As parents, we appreciate the FDA's 2017 Orphan Drug Modernization Plan, as it has provided Luke and all CF patients and caretakers optimism. Allowing drugs to get to market sooner allows Luke and all people with CF more time to live. While Luke is becoming cognizant of the fatality of his disease, for the first time in his life we can look into his eyes and tell him we are confident there will be a cure or at least control for his disease within his lifetime.

I thank you for your time here today.

Jane Mitchell

Hello everyone. My name is Jane Mitchell and I am a mother of two amazing kids, Grayson and Hannah. Grayson is nine, he does not have CF, but Hannah is seven and she does.

My family's journey with CF began soon after Hannah's birth. Like many others, we had no family history of CF. The day was May 23rd, 2011 when Hannah was born. But within seconds she was taken away. Instead of holding my newborn, it was replaced by flashing lights and alarms triggered by a doctor who raced out of the room.

After what seemed like eternity, I was rolled out of surgery to meet Hannah. We signed forms, we took pictures of the three of us in case this was the last time we could ever be together.

We learned that Hannah's intestines had ruptured during birth and she nearly died. At the time I had no idea that this was called meconium ileus, a blockage of the intestines which is a common sign of CF.

After nine days of healing, we got the call. Hannah was ready to come home. I felt joy and relief to finally have her first newborn outfit with me as we walked into the NICU. A random doctor walked by and announced, "your daughter has cystic fibrosis." I had no idea what CF was, but I'll never forget my husband's horrified face. My joy and relief quickly turned to grief and fear.

And so CF entered our lives, along with its many complex physical and emotional impacts. Hannah was turning 5 when her health started to decline. Wheezing started to develop and her lung function started to weaken. We were terrified. We had many tests done at Clinic and were told Hannah's lung disease was progressing and there was nothing we could do. We headed for the beach for family time as we needed to escape. Upon our return we finally found out that it was her allergies were accelerating her decline. We learned the hard way that allergies get dangerous for a CF individual if not treated and/or avoided immediately. With so many burdens we face on a daily basis, this day we gained a new one which greatly interfered with Hannah's love for animals. We immediately had to give away her Kitty that has been with her since birth.

Going to the CF Clinic is good for Hannah, but has a different kind of challenge...it's an overwhelming stressor for parents. When we are asked about all we do to keep our child healthy, we are forced to question ourselves as parents: is it our fault when Hannah's BMI is not where it should be? Were we irresponsible if she caught a bug? What could we have done differently? Are we failing our daughter? These thoughts are constant.

What should be fun becomes stressful: should I let her go to the birthday party if I think another child is sick? What is worse – her getting sick, or her feeling isolated and different? This is our norm, our everyday, racking our minds over every little decision, questioning if it was the right one.

One decision we had to make was a sad one for our family. We started a tradition with a large group of our friends. Every Memorial Day weekend we went camping together at Big Sur. Our spots were reserved in advance so we can guarantee our awesome weekend together. We went hiking, we created amazing feasts over the fire that Sunset magazine would die to have pictures of, all the adults planning their ghost stories for Hannah and Gray. Our last trip had to be our last one though. We had to inform our friends that we could no longer be there with everyone, and they were so bummed. It was the result of the dirt roads near our campsites. When cars slowly drove by or when the kids were just running around and playing, all I could focus on was the dirt being kicked up and Hannah was breathing it in. It was depressing because we knew we were missing out on so much fun, and Hannah and Grayson knew it as well. This is just one example out of so many of what Hannah is missing out on in her everyday life because of this fatal disease.

I want my daughter to have as much of a normal life for as long as possible. My only hope is that both my children grow up and live long, healthy lives. I want Hannah to be whoever she wishes to become. Right now she says she wants to be a Veterinarian and live in a house with many dogs, with her brother's house on one side and ours on the other. I just love that. My fear is that she will never get the chance to fulfill those dreams – for her never to be a Vet, never having a chance of love, or becoming a mom. How destroyed Grayson will be if his partners in crime is no longer around.

Some dream of winning the lottery. My jackpot would be having Hannah outlive me.

Thank you.

Panel: Adults with Cystic Fibrosis

Emily Kramer-Golinkoff, MBE

Tuesday, May 29th, was a gorgeous day. 70 degrees, blue sky, sun kissing your skin, one of those days where the universe was bursting with potential and it was hard not to feel content. I remember sitting outside the Pearlman Center for Advanced Medicine when I got a call that changed everything. "Emily," he said with alarm, "Your x-ray revealed that your lung is partially collapsed in three places." I remember hanging up the phone, looking up at the big blue sky, and then back down at my body, stunned that a body so seemingly functional, could be so secretly broken.

Meeting with my doctor, I learned that there were two treatment options for lung collapse, officially called pneumothorax. A life threatening complication of advanced lung disease. The first was to closely monitor via x-ray and CT to see if time and rest could resolve the collapse. The alternative was a procedure called pleurodesis that involved adhering the lung to the chest wall. The challenge is that it presents complications for transplant, an important consideration for someone with advanced stage disease like me. My hope was to do everything possible to avoid pleurodesis. Ironically, treatment for lung collapse is antithetical to the standard of CF care in profound ways. Mainly no airway clearance and no exercise.

You can imagine the tailspin that throws your head into. The very strategies to which you devote four hours every single day, the ones that you depend on to control the infections ravaging your lungs, they're the very therapies that you must withhold that your collapse might naturally heal. And therein lies the real predicament. It becomes a race. Can you go enough time without airway clearance for your lungs to re-inflate before an infection rages out of control? Lung collapses or infection, which is your poison?

And so on that beautiful May 29th day, I set off on my race against infection. My doctor sent me home on periodic high flow oxygen therapy to re-inflate my lung, my first time ever on supplemental oxygen, and he gave me strict instructions to come into the hospital for admission ASAP if I felt even a slight infection. After a lifetime of treatments piling on, time, rest, and no airway clearance, felt like an evil prescription of omission. I knew enough about lung collapse to know that it was the next step to end stage disease and I felt desperate for information. I plunged into the online CF community. I read story after story of people who experience lung collapses and permanently lost huge chunks of lung function who were unexpectedly thrust into the terrifying world of transplant or even worse, for whom the treatment for lung collapse questioned their future of transplant altogether.

I read of people who had pleurodesis some multiple time and for who it proved unsuccessful. People who told me they were never the same again, for whom that first lung collapse was just the start of many more to come. And I read, time and time again, that the pain of pleurodesis was utterly excruciating. I'm a resilient, hopeful person. All I was looking for was the tiniest glimmer of hope of possibility that it could be okay. But the deeper I probed, all I found were stories of catastrophe or, at best, slow demise.

I couldn't find even one story with a positive ending. The more I learned, the longer the list of restrictions grew. No airway clearance, no exercise, no spirometry, no lifting, and as horrific as they were, I felt I could endure. A lifetime with a disease with a penchant for rearing its head at inopportune times had taught me how to get brutally knocked down and stand back up again. And yet, the one that made me question whether I could endure was the one about joy.

Learning that flying was off limits not only immediately following lung collapse but that it would forever be a major trigger, that was the one that threatened to crush my soul. Even the most unimaginable pain and suffering are

endurable with meaningful punctuations of joy. For me, that joy is traveling to faraway places. The thought that this disease could not only rob my function and my future, but that it could take my single greatest joy that was the part that wrecked my heart, that made me question for the first time in my life, if I could indeed endure.

CF, you take my breath, you take my friends, you take my dreams of a career and a family, you take my hope, my promise, my very potential. You take my future, and now you take my joy.

Gunnar Esiason

Good morning, my name is Gunnar Esiason. I am 27 years old living with cystic fibrosis and a patient advocate with the Boomer Esiason Foundation. Since 1993, the Boomer Esiason Foundation has raised close to $140 million in support of the fight against cystic fibrosis.

For many years I have been known as the little boy with cystic fibrosis on the cover of Sports Illustrated, or the high school kid with CF throwing a touchdown pass on ESPN.

While those moments will live with me forever, they don't tell the whole story.

There are three pillars of cystic fibrosis – Respiratory health, gastrointestinal/nutritional health and mental health.

Respiratory health is synonymous with cystic fibrosis. After all, respiratory decline has killed many of friends who were stricken with CF and continues to give me the most issues.

My lungs are colonized with multidrug resistant Pseudomonas aeruginosa. The hours of daily treatments have gotten more and more difficult to endure, as my arsenal of medications has grown weaker and weaker. I rely on antibiotics of last resort to keep me stable as I anxiously wait for science to catch up with my respiratory decline.

My daily treatments have little changed since I was child in the early 90's. Outside the odd antibiotic switch here or there, my daily routine has looked very much the same for the better part of two decades.

The inflammation in my airways has no acceptable treatment and continues to cause to irreparable fibrosis, which equates to lung function that I will never regain.

Since graduating from Boston College in 2013, I have suffered more than 20 pulmonary exacerbations. That is more than 20 trips to the hospital, more than 20 PICC line placements, and more than 1 year's worth of time on intravenous antibiotics to control my chronic lung infection.

In the months that followed my college graduation, I had to give up my dream of going to law school, I was forced to move back home with my parents, and I was even denied the opportunity to start a career like the rest of my friends until I curbed my decline.

Since then I have worked tirelessly to obtain some semblance of stability. Between maintaining strict compliance with my medications, rigorously exercising, and volunteering for clinical trials, I have made the concentrated effort to do whatever I can to survive.

My gastrointestinal health has also suffered the wrath of cystic fibrosis. In 2010 I suffered from pancreatitis, an incredibly painful and debilitating complication of CF. To treat my pancreatitis I had to withhold food and drink for several days, before slowly advancing my diet back to normalcy. During that time my weight dropped close to 130 pounds. I am 6 foot 3.

I was skin and bones.

In the months that followed, I had a feeding tube placed, and in no small way, my g-tube saved my life.

It has since then shown me the importance of the nutritional side of cystic fibrosis, but more importantly it has shown me the stigma that surrounds feeding tubes – patients hesitate (like I did for many years) to get them placed, and parents feel like failures when they are recommended for their kids.

I now see my feeding tube as a weapon to use to fight back against my chronic condition. I use it to give me strength when I need it most, and energy when I am otherwise feeling sluggish. My feeding tube has helped me supplement my

high caloric needs and serves to nutritionally balance my diet.

My mental health went overlooked for far too long. Prior to a few years ago, no one had ever thought to ask me how I feel about cystic fibrosis. Outside of casual conversation with my doctor during appointments, no one inside the clinic stopped to ask what it was like to be in the midst of more than 20 pulmonary exacerbations.

Why?

It's because we do not have the proper tools to treat and support cystic fibrosis patients dealing with mental health issues.

We do not have a cystic fibrosis disease-specific mental health-screening tool.

Is it shocking that years of medical trauma and declining health have elicited feelings of anxiety, stress, despair, loneliness and pressure?

Since I have started walking down this path to better mental health, I have worked closely with my care team to utilize basic coping mechanisms, and we have had some success. More than anything else, though, I have learned that the three pillars of cystic fibrosis – respiratory health, gastrointestinal/nutritional health and mental health – are interconnected. If one suffers, the rest will suffer.

I know that if I can maximize my treatment and care for all three pillars – staying compliant with my medications and exercise routine, regularly using my g-tube to supplement and balance my dietary needs, and using coping mechanisms to work through difficult feelings – my health will benefit. While cystic fibrosis may be unpredictable, I seek to control what I can. Despite suffering countless pulmonary exacerbations, pancreatitis, and some difficult emotions and feelings, among other complications, I have managed to find some stability. I know that our science is close, our drug development pipeline is more robust than ever and our patient community is motivated.

We still have a long way to go, but for those reasons I am optimistic. There is more hope now than there has ever been for people with cystic fibrosis, and I am happy to continue to play whatever role I can to advance our cause.

Thank you for your time this morning, and Breathe Easy.

Lise Courtney D'Amico

Hi everyone, my name is Lise Courtney D'Amico, I am 24 years old and I live in New York City.

I was diagnosed at the age of 2 with cystic fibrosis after having suffered from malabsorption. I wanted to start off by walking you all you all through my morning routine that I maintain in order to stay alive. Every morning I wake up and I start with what I like to describe as my morning coughs. After having rested all night, my lungs have settled and with that the mucus has built up and settled into my airways. Waking up in the morning requires that my lungs also wake up through a long process of coughing. Sometimes the coughing is so intense that it triggers my gag reflex and causes me to throw up. This is not my favorite way to start the day.

Once my coughing has died down a bit, I begin my treatments. First I start with inhaled sodium chloride. This treatment was actually discovered by doctors of surfers with CF in Australia and it works by essentially adding water to my airways. Next, I take dornase alfa or pulmozyme, which breaks down the mucus bonds so that it is thinner. These two treatments together make the thick, sticky mucus in my lungs easier to cough out. Next, I do my vest, which is a physical therapy treatment to clear my airways. The vest fills with air and then vibrates at a high frequency to loosen the mucus. To me, the most important part of my treatment comes last though. This is where I head to the gym and complete a rigorous workout to help further clear my lungs.

Every day, this morning routine takes between 2.5 and 3 hours. I am human too though. There are so many mornings that I wake up exhausted, but I cannot hit snooze. I have to wake up and do my treatments. My life relies on it.

After completing my treatments, I head to work where I am a business consultant. I love my job, but I am constantly asking myself if I can keep up. The truth is that living with CF is incredibly different than not. Long nights at work for me mean that I am losing valuable sleep that helps me fight off infections and stay alive. But not succeeding at work

means losing the ability I have to pay for medications through the strong health insurance program my employer has.

In addition, explaining CF to an employer is a daunting task to say the least. You risk your employer believing you're not capable and unfortunately, sometimes I think they are right. The truth is that I am out sick more often, I go to the bathroom far more frequently, and I tire more quickly than my coworkers. In addition, there are weird parts of CF that effect my work day. For example, I suffer from CF related arthritis. Sometimes my arthritis is so bad that it is excruciating for me to type, but I have to push through because I don't want to waste a sick day on my hands hurting.

My parents raised me to believe that CF would never get in the way of my future. But every day I grow a bit more weary of that. Yes, the medications that exist today have extended my life expectancy. But I am still not expected to live nearly as long as someone without CF.

I am so lucky to be one of the patients that is benefitting from the new genetic modifier drugs, but these drugs are not a cure. While they have potentially added years to my life, they have not given me a full life. And they certainly have not cured the day to day pain that I face.

I love to succeed at work and I love to think of myself as a normal adult. But the reality is that I am not a normal adult and the treatments that exist today do not bring me close to feeling as if I am a normal adult. Normal adults do not do hours of treatments each more, pop tens of pills each day, face bouts of arthritis at age 24, and have constant stomach pains, all while trying to work.

CF is a scary and progressive disease. As I get older with this disease, I worry about at what point in my life I will become disabled because the medications no longer meet my needs. Will this disability prevent me from achieving the future I hope for – one with a family and a fulfilling career?

I am here advocating for CF research today because we are nowhere near done with this fight. We need medications that will not only extend our lives, but also improve our quality of life through those years.

Thank you for your time today.

Emily Schaller

My name is Emily Schaller. I was born on February 21st, 1982, the third of three children to my awesome parents. I appeared to be a super healthy and cute baby with no immediate health issues but over the first few months of my life I developed chronic ear infections, a lot of runny nose, and was diagnosed with failure to thrive. This was before my second sweat test came back positive for cystic fibrosis.

I was 18 months old when I was diagnosed with CF and the prognosis was not amazing. My awesome parents and myself were told that I would not live long enough to graduate from high school. They were crushed because their cutest baby they've ever seen may not have a future. Immediately in 1983 I was put on digestive enzymes and vitamins to help me thrive and gain and maintain any weight that I could. And they were also told that they would have to perform chest physical therapy, two to three times a day, 15 to 30 minutes each time. Imagine my dad who is 6'7" pounding his little baby for 20 minutes three times a day.

I was 18 months old when I was diagnosed, and my parents were told that I might not live long enough to graduate from high school. Upon diagnosis I was started on vitamins and digestive enzymes to help me thrive, and my parents had to perform chest percussion therapy to help loosen any mucus in my lungs so I could cough it out. We did this 2-3 times each day 15-20 minutes each time.

So this was 1983 and there were not a lot of treatments available. The main symptoms I was going through as a child were more digestive, a lot of bathroom trips. But the main focus at that time was gaining and maintaining any weight. As a child I was super active, always skateboarding and beating my brothers in basketball. Kind of an awesome childhood right.

My first lung involvement appeared when I was in my early teens. It required two weeks of IV antibiotics to treat a lung infection caused by Pseudomonas aeruginosa. I remember checking into the children's hospital in Detroit for these two weeks but I got the news a few days in that I was going to be able to go home and finish the meds at home. So

that was cool, but I did have to do my afternoon treatment at school.

As I got older my exacerbations increased and my lung function decreased, and I also developed allergies to every medication to treat my Pseudomonas. So this required me to go in the hospital and stay for those two to four weeks, two to three times each year. Aside from Pseudomonas, I started to culture MRSA on and off and Stenotrophomonas. My lung infections increased and required me to miss that much school, so I'm missing two to four weeks of school, two to three times a year. I didn't really mind but my parents did.

As my infections increased by lung function started to decrease and my exercise tolerance started to decrease as well. So I had to quit playing basketball when I was I middle school, not because of my height but because I could no longer keep up with the other kids on the court. So my hoop dreams were shattered. I didn't make it to the Olympics.

I began to get super scared about my health and my future because I was watching my CF friends from the hospital die, and my friends who I'd go to CF camp with, die. So the back of my mind, I wasn't sure what my future was going to be.

In my teens new treatments started to come out like Pulmozyme to thin the mucus, Tobi and Cayston came out to treat the Pseudomonas in our lungs, and this added longevity to our life, as you can see in that last graph. Median age of survival started to increase. But I was still scared, and also annoyed because these treatments, like so effective added hours to our daily treatment burden.

In my early 20s I was so sick that I could no longer work full time, so I had to go on social security and disability, just to live, which is not a way to live. Because of my declining health I was missing so much work I was forced to do this. But in 2010, almost nine years ago now, I began a phase three clinical trial for a drug, then called VX770, today called Kalydeco or Ivacaftor and this is the first medication of its kind to treat the underlying cause of cystic fibrosis. It treats one of my mutations specifically, G551D.

Within a few days of taking this medication, it felt as if somebody came from behind, turned on a switch on the back of my neck and said, "This is how you're supposed to live." My quality of life is pretty darn good. My pulmonary function is now 85% from its previous 50 and 60. My coughing is nowhere like it used to be. My sweat, my super salty sweat, is way less salty. My hospitalizations went from two to four times a year to once every two to three years. I bought a house and I started a retirement fund. Life is pretty good.

I started running and biking before I started Kalydeco and it was kind of hard, but with Kalydeco, running and biking is a little easier, so now I push myself to run marathons. I ran my second marathon in May.

So, my future's looking pretty good, but I am scared. I have these thoughts, "what if Kalydeco stops working, what's next? Will my hospitalizations come back? Will my lung functions decline? Will I need a transplant?" I don't know. I don't think anybody knows because we're so new with these new modulators. But there is hope right?
So we need treatments, we need them now, we need them fast. So my friends like Emily and Lise Courtney, and everyone else here can have a retirement fund

Thank you.

Topic 2: Perspectives on Current Approaches to treating CF; Goals for Potential Treatments; Drug Development Issues

Panel: Parents of Children with Cystic Fibrosis

Kat Porco, MS

My name is Kat Porco and I live a life defined in numbers. The most horrifying of which is thirty-two, the life expectancy of my daughter. It has been twelve years since Maylie entered the world. 9, since a name was given to the painful set of symptoms that consumed our lives and perplexed the doctors for her first 3 years of life. On that fateful day, her body was a mere twenty-three pounds of GI and pulmonary distress, her oximeter reading was seventy-two. Two, the number of weeks the doctors hypothesized she would have lived without diagnosis.

Fifteen hospitalizations since her diagnosis, IV antibiotics consuming over forty weeks of her young life. She grapples with four comorbid diagnoses; peripheral neuropathy, asthma, GERD and cystic fibrosis related diabetes.

Procedures flood our lives, making it increasingly difficult to track. 8 PICC placements. 2 PH probes. 2 feeding tube placements. 4 Bronchoscopies. 2 colonoscopies. 1 endoscopy. 1 port placement. 1 fecal transplant. 1 air flight for peritoneal sepsis.

Maylie lives a life that begs her to be strong, in a body that continually fails her. The idea of resilience in cystic fibrosis is the supreme illustration of irony, you need reprieve from pain in order to find resilience, do you not? I question how can we continue to break and not be broken.

Each upcoming procedure begs of me an emotional triathlon of strength and support. I await the moment when a procedure is announced in her presence, I watch as her spirit visibly breaks through her eyes. While not the most horrifying of procedures, her first PH probe will be forever embedded in my memory.

Her eyes dart rapidly, like a wild animal, scanning for potential predators; they land upon mine, only for a second. Her face is a reflection of the fury that exists within, her inability to trust anyone -- even me. I reach for her with motherly compassion, and she pushes me away. At twelve years old, she has learned distrust from the countless similar moments that have flooded our lives since her cystic fibrosis diagnosis. Today she sees me as an enemy, as much as any unfamiliar nurse who enters her room, maybe even more so.

Maylie's cynicism for me is grounded in experience, that reality is harrowing. She knows that, when necessary, I will abandon the maternal commandment to protect her. Her distrust has come from countless procedures associated with her CF. Although I understand that they are all necessary and for her greater good, she has experienced fear, pain and distrust. She has learned that I will betray her through my participation.

She knows that if the situation deems it, I will be forced to ignore her screams and perform a role in which I seem almost robotic. I hold her down, attempt to calm her, and worst of all, I consent. I consent to her body being violated, her wishes being ignored and her all-important voice unheard. She is no longer a person. She is a patient.

After the procedure, she looks at me in disbelief. She stares deeply, reaching into my soul and then she asks the question I silently begged her not to ask, "Did you know they were going to do this to me?" My eyes well, my heart sinks. I nod feeling the fear of my admission. Her eyes squint from the pain of betrayal, and she says, "I hate you for this." Any small ounce of strength that I was able to muster up for this day has been depleted three times over. I sob like a child, apologizing over and over. The nurses try to console me, explaining that she doesn't mean it. And while I want the reassurance, their words are useless. I have failed her. She was in a living hell, and I did not save her from it. I could not.

The following week, I grappled with immense sadness. I lost my former self; I was simply a shell, walking blindly into the unknown. A part of me died that day, and rebirth of that fragment of my soul is impossible. There is no greater instinct than a mother's need to protect, and I have had to willfully disregard it countless times.

Through this journey, I have learned that protection is redefined in chronic illness. It is often making choices that are painfully unfair; choices that will make us betray our own children. However, it is our strength that commands us, otherwise we would run. Every part of my being screams to flee the procedure room, but I stay, hoping that my presence brings Maylie even one second of calm.

I balk at this CF fight, for it is a fight against time, not steadfastness. For if dedication guided this journey there would be no question, we would prevail. But the unfairest of truths is that nothing in CF is based in reciprocation. We put in endless hours of therapies, countless drugs enter her perfect, undeserving little body, often in rapid succession. However, nothing stops the inevitable at this point, so we wait, not so patiently. We hold tight to the promise we hear so often that we are stronger than we feel.

Thank you for listening to our story and considering us when faced with decisions around cystic fibrosis.

Jen Caruso

My name is Jen Caruso and I have a 16-year-old son with cystic fibrosis. From everything you heard so far today, I think we can all agree, living with CF is not easy. It is scary, as you never know which lung infection will cause irreversible damage causing permeant loss of lung function, or worse, leading you to transplant or death.

Let me explain a typical day in the life for Michael. Michael gets up every day before school at 4:30 in the morning. He must complete a 1-hour breathing treatment to start his day. This consist of 3 inhalers, plus 2 to 3 other inhaled solutions through a nebulizer, plus being hooked up to a Vest, to help break up the mucus. He does these breathing treatments at least 2 times a day, and up to 4 times a day when he has an active infection. In addition to the breathing treatment Michael takes over 40 pills a day, every day. When he has an active infection, that increases with additional pills to take or IV antibiotics.

Two years ago, Michael was facing a long-term treatment for bacteria he has in his lungs. It's one of the bad ones, called AFB (acid-fast bacilli). This treatment would mean up to 9 -12 months of IV antibiotics which come with all sorts of side effects including hearing loss. We have heard that around 80% of those with the treatment end up with hearing aids. Liver failure is also a potential side effect.

After long hours with his medical team and understanding the risk of not treating (which we are told is death or transplant, although insurance will not cover transplant if you don't 1st try to treat with this method), the decision was made to treat.

Michael asked for "a kick ass summer" before we would begin. He wanted one last summer to not be hooked up to IVs, one last summer to have his hearing, and one last summer to feel like a kid. Well after the summer we tested Michael's lung function and he went up; not by much but it went up. The doctors decided we could wait, give Michael more time with his running and being active, as well as to see if the some of the new medications we had him on could build enough strength and continue this upward trend. It's working; the treatment is now on the back burner…. for now.

While it's great we have that treatment on hold for now, the bacteria are still in his lungs. We need better options, options that will allow us to treat the infection and not harm other parts of his body. We need things like an antibiotic that is localized to the lungs only, to minimize these side effects. We need more medications for inflammation and overall more medications that do not have harmful side effects where we trade one problem for another.

We are in a race against time and with each new advancement in medication coming to the market we see improvement in Michael quality and quantity of life. I see improvement in his overall mindset about having this disease, but most importantly I see a future for my son. I see hope. But the fear is still there, every day. The fact remains we have no cure or long term treatments. The fact is CF will take my son still at a very young age.
In one of our most difficult conversations around life expectancy, Michael said to me, "Mom do you know what my biggest fear is?" I said, "Is it losing the battle to CF?" He said, "No, it's dying without ever knowing what a normal childhood should feel like."

So while I cannot turn back time, I can keep fighting for him and for everyone else who suffers from this disease. We can all work together to bring new therapies to market that will ensure that he knows exactly what a regular adulthood's going to feel like. An adulthood where he's not hooked up to breathing treatments or taking 10s and 10s of pills a day. An adulthood that allows him to go to college, have a family, and someday even possibly being the lawyer that he wishes to be.

Thank you.

Joey Klausing, JD

Good afternoon. I am Joey Klausing, executive director of Cure CF, a small non-profit in Louisville, KY. I am also a partner in a law firm, but my biggest job or responsibility is making sure my 11-year-old son Luke outlives me!

There are no off days for cystic fibrosis. This morning, I read how the players from the Baltimore Ravens and Washington Redskins will get today off to recover from yesterday's games. Let's contemplate that concept for a

second: The world's fittest athletes get a day off from training after they participated in approximately 60 to 80, 4-second plays. That equates to about 4-5 minutes of game activity.

While these premier athletes were sleeping, Luke arose at 6:00 a.m. this morning to commence his treatments. Just as he has done for the previous 4,203 days. It starts with 15 minutes of hypertonic saline followed by 10 minutes of Pulmozyme, followed by 30 minutes of chest percussions, followed by nasal sinus rinses, followed by 2 sprays of Flonase, followed by 2 sprays of Astelin, followed by 4 puffs of Advair, followed by 20 mg of Prevacid, followed by 30,000 units of Creon, followed by 1 ¼ capfuls of Miralax mixed with water, followed by 2 pills of Orkambi, followed by 1 pill of Prozac, followed by 300 mg of Ursodiol, followed by 40 mg of Straterra, followed by 20 mg of Zyrtec, followed by 1 probiotic which is followed by vitamin gel capsule.

The time is now 7:30 in the morning, just 90 minutes later.

Without these pharmaceuticals Luke would not be alive.

Luke often becomes frustrated when he is forced to do his treatments. My wife and I balance "letting him fail" with the need for his treatments. Over the past year, mental health issues surrounding cystic fibrosis have become more prominent with Luke. A 30-minute treatment in the afternoon stretches out to almost an hour as Luke stalls and turns the machine off numerous times. This fosters anger within the household, as Luke views his parents as the people who make him do the "not fun things." Luke also has rebelled against taking his medications, as his sister, friends and classmates do not take them. He just wants to be normal.

We have been to Capitol Hill numerous times as a family to discuss the importance of funding for cystic fibrosis research. Our Senator is Majority Leader McConnell, and we had the opportunity to meet with him again this past June. As you all know, it can be hot in DC in June. Well the Senator's office was hot, and Luke became so uncomfortable he took off his suit jacket, shirt and tie, right in front of one of the most powerful people in American government. I bet that was a first for the Senator! While that may be a comical moment, it still highlights the struggles CF kids go through. Even on those trips, we must plan breaks to return to the hotel to perform Luke's treatments.

Lastly, I want to stress to the audience the urgency that is needed. I believe most here are 37 years or older. Luke's life expectancy is 37. Accordingly, if any of you had cystic fibrosis, the odds are you would not be alive, yet alone in attendance. Each day that a drug is ensnarled with regulations and bureaucracy, is one less day that Luke and all other CF patients have to live.

Thank you.

Arek Puzia, MBA, CPA

My name is Arek Puzia, and I am the father of Natalie, a 4-year old with cystic fibrosis. Like some of the other panelists, what makes Natalie unique is that she has one of the rarer mutations. She is homozygous for CFTR deletion two comma three, which is essentially a 20,080 base pair deletion within the CFTR gene.

So this is a class one; no protein is created, therefore although we're very happy about all the medical breakthroughs that have happened over the last five years, none of them really apply to Natalie. There are no clinical trials currently in place that she would qualify for, and so while we look on with hope, it's a very challenging process.

Currently most of the medications she uses were developed many years ago, over a decade ago, and that's really what keeps her stable and going.

We found out about Natalie's diagnosis through the newborn blood test in California and received the results about 2 weeks after taking Natalie home from the hospital. With no medical history of major disease, and pre-pregnancy genetic testing that came back completely clean, we were shocked and devastated. In one phone call, one moment, our lives were completely flipped on their heads. Instead of rocking our crying baby at night and being annoyed and exhausted parents, we had to wake up at 4am every morning and beat our tiny baby with a plastic cup to try and clear her tiny lungs.

Currently, at four and a half, Natalie wakes up before most kids do. She has to begin a routine that at minimum,

happens twice a day, and often when she catches a cold or flu, will happen four times per day. She starts off by taking two puffs of Albuterol, then she must take a break in order for that to take effect. We then hook her up to the vest machine, and fill up a nebulizer with hypertonic saline solution and she sits there for about 15 minutes. It's a challenge sometimes to keep her on it for 15 minutes. The saline burns her sinuses and her mouth. She doesn't want to do it. We have to control her and do all sorts of creative things, and that last for about 20 minutes and we also have to finish off with Pulmozyme after that. So each process takes, at minimum, 40 minutes and that's twice a day when we're, again like we said in our healthy state, when nothing is happening.

Following this whole process, we need to feed her, which again for those of you who have small kids, it's a challenge in itself but this is extremely important. She rarely has a BMI over 50%. Most of the time she falls somewhere in the 30s, so eating right now is extremely important. In order for her to have a full meal, whether it's breakfast or lunch, she has to swallow eight pills before that meal. She actually quite a rockstar at this at this point. And all of this is simply to maintain rather than improve her health.

We have to do regular visits to the doctor, in fact this morning she did saw her doctor on an off visit. The hospital visits and the doctor visits are not only time consuming but extremely stressful for everyone involved, especially for a 4 1/2 year old. We have to do annual labs. The labs for a 4 1/2 year old take about a minute. We need about six or seven vials for all the different lab test that are ordered. That minute feels like three hours, or like one of my friends like to say, "Two minutes while on fire."

Every cough that comes from Natalie sounds scary and reminds us that there is something very wrong in her body. We have extended family in Europe that we have been unable to travel to visit because having a 4 1/2 year-old on a flight that long, and with all the equipment that we have to bring across, and all of the contingencies that we have to put in place is just not realistic. So she has family that she has never met, and at a time like this that would be really the most important. To have these loving people around her that she is being kept from.

They say that having cystic fibrosis is like drowning from the inside. Well, as Natalie's dad, the feeling I have is like watching my daughter drown while being behind the fence that is far too tall for me to get over. It's not a fast drowning, it's something that I sit there and watch every single day, minute by minute.

Our lives have completely become revolving around this disease. We've scaled back careers. We've put plans on hold. Natalie's our only child, it's possible we will not have other children. We have to think about not only our own futures and perhaps a retirement, but also design something where we can help Natalie because as you well know careers are very challenging, so we must be able to cover her living expenses, be able to pay her medical costs. Our insurance premium is $43,000.00 per year, right. It's a pricey, pricey disease on top of everything.

From my perspective I would really ask the FDA to consider what this feels like to watch your child slowly drown from the inside. We would really like to see focus coming from the industry and the FDA on driving down the burden of these treatments, so maybe instead of hours per day for Natalie we can get it down to 30 minutes or less per day. Even that would be a tremendous help. We would also like to see some novel medication that come because about for these mutations where the things that have come around over the last few years simply do not help.

So certainly the genetic parts of it, we are ready and willing to take on trials. We are willing to take on risks. We understand what they are. We have amazing doctors and amazing team that works with us. We are willing to learn what the risks are and take those risks. We know things can go sideways, we're okay with that. We'll take those calculated risks so that she may have a future and some potential.

Thank you for your time.

Panel: Adults with Cystic Fibrosis

Emily Kramer-Golinkoff, MBE

Good afternoon. Thank you to CFRI for having me here today. I'm back this afternoon starting with some background. I'm 33 and from Philadelphia. I have a Master's in Dialectics and my professional background is nutritional health. I also have cystic fibrosis. I'd argue that the craziest part of this disease is its sneaky perceptiveness. You would probably

never guess that I have only 31% lung function, and I take over 30 pills, do countless insulin shots for CF-related diabetes, and spend roughly four hours a day on breathing treatments and airway clearance just to stay alive.

Daily medications range everything from bronchodilators, inhaled an oral antibiotic, mucociliary clearance, digestive enzymes, so things like short and long-acting insulin, vitamins, and the list goes on. When I'm sick, I go into the hospital for week long courses of IV antibiotics. There are no breaks, no days off.

And yet, if discipline and hard work were all it took, surely, overachiever me wouldn't find myself dangling on the verge of end-stage disease, where the only treatment is lung transplant, and even that is an uncertain road. This monster of a disease has a mind of its own, ravaging my body despite my hardest attempts to stop it.

Fortunately, in 2012 hope arrived like never before, with a monumental approval of a CFTR modulator, the first drug to treat the root cause of CF for 4% of the CF population.

In 2015, that number expanded to 40%. I now was excitingly triple combinations in Stage Three trial, but numbers expected to balloon to an astounding 90% of the CF population in the next couple of years. Unfortunately, with two copies of a rare form of CF caused by a nonsense mutation, I am here to put a face to the outlying 10% that won't benefit from any of these breakthroughs, to underscore that the job is far from done.

There are 7000 of us still waiting for whom this disease remains the same killer that it was before 2012. We are the orphans of this orphan disease, still stuck in prehistoric CF times, as our CF friends get their game changer, and we are the ones left behind. We are still waiting, yearning, gasping, pleading for something, for anything, so we can hold on. Our heart's happy for our CF friends, but desperate to join them.

Back in 2011 my disease was progressing, and it became clear that science wasn't going to deliver a breakthrough in time to save my life. It's from that place of desperation that we started Emily's Entourage, a 501C3 that raised millions of dollars with one singular goal: accelerating research and drug development for nonsense mutations of CF.

We are working with our heart and our soul for everyone with a nonsense mutation and everyone who loves them, because having modulators for 90% of the CF community is remarkable, but it's not good enough. With a progressive disease like CF, time matters. I am here today with a desperate plea: please remember that the job's not done yet. There are 7000 of us waiting, desperate to have careers and travel the world, to plan for a future that we can actually believe in.

I feel the crunch of time with every breath I take amongst the propeller at Emily's Entourage for everyone trying so hard to survive with this disease. FDA, we need your ingenuity and partnership to develop new paradigms that can speed race the breakthroughs of tomorrow. For patients with untreatable mutations and particularly those with advanced stage disease, the status quo is fraught with danger.

Continuing down this path, this disease will kill us with certainty. We need you to prioritize drug reviews for people for whom waiting might be the difference between life and death. Even drugs with a potential for risk in the future are bets we're willing to take for time we'd otherwise never have.

And so as you dive back into your work tomorrow, I ask a few things of you. Let's finish the job not for 40%, not for 90%, but for 100% of the CF community. Let's take little wins and not be greedy, and still strive for forever cures. Perhaps most importantly, let's do it all faster than fast, because my life and lives of so many others like me hang in the balance because time is of the essence, and the clock is ticking, ticking.

Most of all, because all of us, even those with those with nonsense mutations, we deserve hope for a future, and a world where we'll all breathe easier. Thank you.

Lise Courtney D'Amico

Hi everyone. My name is Lise Courtney D'Amico and I was diagnosed with cystic fibrosis at the age of two after suffering from malabsorption. I have been fortunate enough to participate in many clinical trials throughout my life. These trials have ranged from taking anti-inflammatory medications to test for lung function improvement, taking a new kind of digestive enzyme to test for weight gain, inhaling new medications to help clear the mucus out of my

lungs, wearing a new sodium chloride sweat test device to test for improved accuracy, and many more.

Unfortunately, none of my completed trials have resulted in a new medication for the cystic fibrosis community. While all of the trials I have participated in sound very different, they hold one thing in common. That is that they are incredibly time consuming. I live an hour and a half from my CF clinic so I spend 3 hours traveling to and from the trials and then the trials themselves often involve hours of sitting around at the hospital. But, when you talk to me or any other CF patient about what it is like to participate in a clinical trial, it is like we have won the lottery.

Yes, clinical trials require the patient to spend more time at the doctor and to devote extra time to treatments, but that all does not matter when we consider the possibility that this could make life with CF more bearable.

The truth of the matter is that the reason that CF patients are so eager to give up parts of their lives for medical research is that we are absolutely desperate for a cure or for medications that will improve our quality of life today.

In fact, at times the clinical trial environment feels almost competitive. All of us SO badly want to devote our time and bodies to the mission of finding a cure for this disease. Every patient wants in on the chance to take the next best medicine. To get into the trials and you must watch the Cystic Fibrosis Foundation website carefully to see when to call your doctor and ask if you are eligible to join the trial. It is evident from all of the cystic fibrosis patients here today, that we are devoted to finding a cure and the truth of the matter is that this drive for a cure comes from the fact that living with cystic fibrosis is hard.

I have been so fortunate to qualify for Symdeko, the latest CFTR Modulator drug. This drug came to market through a long series of clinical trials that I so badly wanted to join, but I was not able to get into. But, there are so many other cystic fibrosis patients that are not eligible for this medication.

My best friend is a fellow CF patient who lives in California. She lives with a nonsense mutation, which means there are zero drugs on the market for her specific mutation or class of mutations. While I celebrate my success on Symdeko, I cannot forget that despite the fact that we suffer from the same disease, my best friend's life looks very different than mine. She does not have the optimism of Symdeko, in fact she does not even have the hope for her future knowing that there are successful drug trials in the pipeline that will benefit her. Instead, she is just waiting.

Every patient dreams of the day that we wake up and can take an unhindered, deep breath. In fact, when my peers ask me what it is like to have cystic fibrosis, I want so badly to ask them what it is like to take an unobstructed breath. Instead of dwelling on this, I participate in trials. These trials are the hope for my future.

Yes, we are all well aware of have the median age of survival for cystic fibrosis has increased over the past 10 years. But I still watch my peers pass away from this disease almost monthly. And if that were not enough in itself, frankly I strive to live past 42. My mother was 41 when she gave birth to me. I like to believe that meant her life was just starting. I don't want mine to end then.

There is still work to be done for even those with the most advanced treatments today. I pray for new medical trials in the future that result in treatments that aid my complicated digestive issues, that give me answers to the medical mystery that is CF related arthritis, and that allow me to take a deep breath. Clinical trials are the path towards a future for me and my peers with CF. I am here advocating today truly in hopes of guaranteeing myself a long future without the burdens of cystic fibrosis.

Thank you for your time today.

Anna Payne

Hello Everyone. My name is Anna Payne, and I am from Bucks County, Pennsylvania. As an Adult with cystic fibrosis, I'm honored to be here today.

When I was born in 1987 the gene that causes CF had not yet been discovered, and my parents were told I would not live long enough to graduate high school. Yet here I am 31 years later. These years weren't always easy and if it wasn't for the advancements in treatments and therapies I wouldn't be here today. Let alone be engaged and own my own home.

Every day requires 3+ hours' worth of breathing treatments, which consist of 4 inhaled medications and 45 minutes of chest Physical Therapy which is administered by my mechanical Vest that shakes me to loosen mucus. I take over 30 pills a day to help digest my food, which, as I will share in a moment, do not always help me. I also take approximately 10 other pills. **This adds up to nearly 14,000 pills per year.** All of this to try and slow my health decline - the time involved with my daily regimen increases dramatically with every lung infection. When I was born I spent the first year of my life in and out of the hospital - I have been hospitalized 15 times in my life.

My main issues stem from my digestive system – obviously my breathing has always been impaired but my digestive issues caused me more time missed from work and nights home. When I was born I had Meconium ileus- which is a bowel obstruction that required emergency surgery. I have giant Scars across my stomach- from not only the surgery but the two colostomy bags I had for the first 6 months of life. I had blockages when I was younger that caused long hospital stays. I recall these stays vividly as they required a large tube to be inserted down my nose and into my stomach as well as various colonoscopies. My daily regime to curb my chronic stomach pain and discomfort, includes 6 medications. I have lost count of the amount of time I have missed from work, school or social functions because of my digestive issues.

The older I get the more I can feel the negative impact of this disease. I can feel when I need to do my albuterol- growing up it was just 2 times a day because it was doctors' orders now its 2-3 times a day because I can't function without it. The chest tightness and the coughing fits that occur if I wait too long between doses have been playing a larger part in my daily routine. Sometime I even need a middle of the night dose. I never take a full night's sleep for granted- If I make it through the night without a coughing fit, it's a miracle.

It is a horrible feeling knowing that your body is failing you. I can feel the decline. The impact the progression of this disease has on me physically can be measured by FEV1 scores and BMI charts, but the impact it has on me mentally is hard for others to comprehend. CF is a challenging and isolating disease. I have lost many friends to this illness. This takes a toll on me. I now see a psychologist to help treat the impact CF has on my mental health.

A majority of the medications I take are to help keep my lungs clear and prevent them from getting infected, and the CFTR Modular helps try to slow down disease progression. Without these therapies, I truly believe I wouldn't have experienced an increase in lung function and weight gain. I wouldn't be almost 4 years shy of my last hospital admission and IV treatment. I went from having frequent pulmonary exacerbations to not having one since 2014.

Recently, I have been having some liver issues just adding another broken organ to the list – I had a liver biopsy which was inconclusive- and provided no immediate treatments or answers. Dr.s aren't sure if they will ever know the cause of my elevated liver enzymes. While most people my age are touring the new craft brew spot or winery in the area- I can no longer participate in those activities because my liver can't handle it.

Prior to starting Symdeko in February I was on Orkambi. I actually participated in the clinical trial for that drug for over a year. It required 4am blood draws almost weekly for the last few months. I wanted to make sure the trial didn't interfere with my job so I would get up super early, as the trial required an extra hour of driving. At no point did I think about giving up on the trial because I knew that this medication could help keep my friends alive longer. I had to use my vacation time from work for some of the appointments, but I didn't care. To me if these medications got approved then there would be more time for vacations later. I had blood draws every couple of hours, EKG's and pulmonary function tests. Nothing was too complex but all vital to making sure a life changing medication could have a fighting chance for approval.

I know that these new treatments are helping me and many others, but they are not a cure. We deserve the chance to live out our dreams-to be productive members of society.

Isabel Stenzel Byrnes, LCSW, MPH

My name is Isabel Stenzel Byrnes, and I am 46 years old, from Redwood City, California. I was diagnosed with cystic fibrosis, along with my identical twin sister Ana, at birth. Like the stories of our pediatric panelists, we endured malnutrition and chronic pneumonias. We did chest percussion treatments that took five hours a day throughout our childhood.

We endured multiple hospitalizations, so by 18, we had spent 36 weeks in the hospital. Antibiotics saved our lives for many decades, but our bacteria in our lungs became more and more resistant. It took days to weeks to feel better after an IV tune up. New antibiotics were more important than ever. Oral Cipro helped us stay out of the hospital for our sweet sixteen birthday party, until I became resistant to it. At 18, I started enteric coated pancreatic enzymes, gained 30 pounds and finally went through puberty. Ana and I participated in the clinical trial for Pulmozyme, a mucolytic. Ana received the drug and her lung capacity increased within days from 40% to 55%. I didn't feel any difference, as I had the placebo. When the open label drug became available, my lung capacity increased from 50 to 70%. We were able to graduate from Stanford, live in Japan for a year, and complete graduate school, still with intense effort with adherence to our treatments.

Despite our obsessive compliance, a downward progressive spiral of lung infections eventually destroyed our lungs. I coughed up blood regularly and nearly died from two massive hemoptysis episodes; bronchial arterial embolizations saved my life. We could no longer wait for additional drugs. Transplantation was our only hope. Ana received a double lung transplant in 2000 at the age of 28. She received a second transplant in 2007 at 35 due to chronic rejection of her lung, despite her extreme adherence to her medications.

I wish there were better drugs for transplanted CF patients, specifically drugs for chronic rejection or bronchiolitis obliterans syndrome (BOS). This is a deadly disease that can spiral very quickly into lung failure; there is no treatment at all. Second transplants are extremely rare and high risk. There are approximately 250 CF patients receiving a lung transplant each year, with about 1500 CF lung recipients living (according to the CFF Patient Registry in 2016). 25% of CF patient deaths are lung transplant recipients.

When I was 32, I went into lung failure and was put on a ventilator. The breathlessness and suffering I experienced at the end of my life with CF was something I pray no one else ever has to ever go through. One day after being intubated, I received donor lungs just as I was about to enter a coma. You can see how damaged my CF lungs were here. Of course, Ana and I are so grateful for our organ donors.

Today, I take 35 medications daily to survive. I am immunosuppressed and have to be very cautious about exposure to germs. Every day I fear rejection, cancer or infection. I have had five skin cancers removed including one extensively spread in my eye. I flush my sinuses daily to limit sinus infections. I endure chronic intestinal blockages and depend on GI motility. I exercise very hard to be an athlete, to celebrate my lungs and to help with bone health, constipation, diabetes and muscle strength. My CF-related diabetes is my greatest daily struggle with blood sugars between 40 and 350. I must monitor my kidney function as my transplant medications are nephrotoxic.

Because the CF gene increases the risk of GI cancer, my mother developed colon cancer at 56. She survived, but when my sister was 38, she was diagnosed with stage 4 small bowel cancer. This was caused by her CF gene as well as her double immunosuppression following two transplants. Ana fought cancer bravely but died at the age of 41 after immense suffering and absolutely no available treatment for small bowel cancer. I wish there were better drugs and diagnostic procedures for CF-related GI cancers.

As a half Japanese, I am living proof that ethnic minorities can have cystic fibrosis. I have one F508 from my German father and a R347H-979A mutation from my Japanese mother. We have unique genes and my hope is that some of the gene-targeted drugs will include mutations that are common in minorities.

I now work as a social worker, to give back. I'm blessed to be alive thanks to advances in CF drugs and transplantation. I love my life but I am not a victim. But I grieve that I could not survive to benefit from the gene-specific modifier drugs that are no long relevant for my transplanted lungs. Please remember the transplanted CF patients are the orphans of this orphan disease. We need new drugs to reduce the risks of cancer and infection, and to treat chronic rejection or BOS. We want to keep living and have a future just like all CF patients.

Thank you for listening.

Appendix 8: Emailed Comments

Comments Submitted Via Email: Externally-Led PFDD Meeting on CF:

Topic 1: Disease Symptoms, Challenges and Impact on Quality of Life

From: Melissa S., adult with CF
Re: Gastrointestinal Symptoms

I suffered terrible pancreatitis after taking tetracycline. I had to fly home from college and spent a week in the hospital on IV liquids and pain killers.

From: Paul Q., adult with CF
Re: Lung Exacerbations

Hemoptysis controlled only after lobectomies in my case.

From: Fran H., grandmother of a child with CF
Re: Mental Health, Burden of Care, Clinical Trials

I'm writing these comments in response to the FDA Webinar on October 29, 2018. My granddaughter, Megan Reveles, was diagnosed two years ago at the age of nine with CF. As you might imagine, this was very hard for her to process at the time and it would prove to be increasingly difficult for her as days and months passed. CF affects all tissues and organs, and it is a difficult task to try to find just the right medicines that will address each individual's symptoms.

The medications Megan must take are adult doses and they often make her feel ill, and they are very taxing on her small frame and systems. She tries not to complain, but some of the treatments hurt, some give her headaches or stomach aches, and some hurt her joints, to name only a few of the affects her treatments have on her.

Her treatments take about an hour and a half and include using nebulizers, inhalers, wearing a percussion vest, taking vitamins, sinus rinses, sterilizations of her equipment, and more. She must awaken early enough each day to be able to complete these treatments before she can go to school. She must complete treatments at least twice every day of her life. If she is coughing or has sniffles, she must do an extra treatment or two. If she is sick and really not feeling well, she has to somehow tolerate even more and longer treatments. On some days it is quite difficult to fit it all in, but she does it. This is part of every day for her now, whether it is a school day, a summer day, a holiday, or a day of vacation. It is always there. There is never one day that she can go without. She tries so hard and she does all she can to help her body stay as healthy as possible. She works hard on her grades at school and she is a great little student. She also plays sports, usually a few times per week, fitting it in as time will allow. CF has impacted every aspect of her young life. This is her life now. In portraying this brief snapshot of my granddaughter, please keep in mind that my description of Megan and her condition only scratches the surface of what she is experiencing and enduring.

The long hours and painful treatments that Megan must endure to take care of herself is only part of the CF picture. I often wonder how tormented her young mind must be. Most young children look to their futures with expectant enthusiasm even though they are uncertain of what their futures will bring. A CF child's mind knows the uncertainty of their illness and while looking to their futures as any young child will, CF encompasses her every dream, every moment, it is always there.

In addition to the trials and tribulations that a CF child must bear, this is a "whole family" diagnosis. I have watched Megan's parents and siblings as anguish and fear gripped their everyday sense of reason and routine and shattered the picture of life as they knew it before this diagnosis. Megan's parents and her brother and sister were all trying in their own ways to make sense of this new life they must now all lead together. As with any difficult situation, they faced it squarely and struggled to find how the pieces of this would fit together. This is an amazing family and each family member contributes for each other and for the benefit of the family as a whole. Even though I could relate many, many situations that tested this family in unfathomable ways, my explanations would only be a meager hint of what they have gone through to find firmer footing and a way to find a bit of normalcy in this new role that was thrust upon them.

Megan has had the opportunity to take part in trials for CF. Fortunately for Megan and her family, their insurance coverage has made it possible for Megan to continue with a specific medication that has made a significant and positive change in Megan's health. While we are very grateful that Megan's family can provide this insurance for her, their insurance does not cover many of the essential items such as antihistamines, laxatives and stool softeners, vitamins, sterile wipes, cotton

swabs, antibiotic ointment, sinus rinses, or many other items necessary for Megan's daily care. The costs for these non-covered medical items over days, weeks, and months are quite expensive.

For many people with CF this presents an insurmountable predicament as it is very costly to purchase their many over-the-counter necessities and they do not have insurance that will allow them to continue beneficial medicines after trials have been concluded. This very often results in loss of health for daily living and quality of life, compromised or impaired physical health and longevity, and depression and loss of hope. For those with CF, including Megan, taking part in trials and finding new and better ways of managing this disease is paramount.

I pray daily that researchers will be able to find more effective ways to treat CF. My ultimate hope and dream is that a cure will be found, and that it will be found in the very near future. Until then, I eagerly await better medicines and better methods to treat Megan's symptoms and help to keep her as healthy as we can. CF is the most common fatal genetic disease in the United States. I implore the members of the FDA to keep a sharp focus on this population and the magnitude of this multifaceted disorder as I believe that each corner we turn brings us a little closer to truly being able to help those with CF. I thank you and I very much appreciate your time, effort, and consideration for those with Cystic Fibrosis. Please contact me if I may be of further assistance.
Respectfully, Fran Hutton

From: Jessica L., adult with CF
Re: Multi-Systemic Impacts

Comments for the FDA on multi-system impacts of living with CF from an adult perspective. Sorry for the long email, but I hope this sheds some light on what life with CF is like.

I would like to piggy back off of all that others have said. I am a 29-year-old female with Cystic Fibrosis and CF Related Diabetes with a lung function of 42%. Here's some background on my life living with CF. Due to many other lung exacerbations, I continue with each illness to lose precious lung function that I am unable to regain. CF has a multisystem impact. Not only do our treatment regimens dictate our entire day, but causes lots of fatigue, anxiety, increased lung decline, pain, shortness of breath, isolation, financial stress, difficulties with work or school obligations, CF related diabetes, family planning issues, etc. There were days when before I left for work two hours after waking up to do my treatments and eat a nutritious breakfast, I was completely exhausted from coughing and felt like the days I went to work I was severely fatigued before ever arriving,

I suffer from lots of anxiety around various topics that of themselves are issues I deal with because of CF. I have anxiety about infections, about dying but more about how my family will deal with my death, struggles with falling asleep and staying asleep, trouble keeping good blood sugar control as my insulin needs are constantly changing based upon infections my body is fighting, struggles with not being healthy enough to carry my own baby and on the flip side the significant financial struggles of the costs of surrogacy, pain that comes with significant coughing including herniated lower discs and back aches, GI problems with constant bowel changes, gas, and stomach aches, inability to participate in certain extracurricular activities due to shortness of breath, the list could go on and on.

I think insurance companies dictating our care is a whole other issue. We aren't just like everyone else, yet they want to treat us that way. I could go on and on about my struggles with insurance companies to cover certain CF related things or the financial burdens that come with needing to use that coverage. Most insurance companies throughout the country don't cover surrogacy or adoption, yet it would be detrimental to women with CF to carry their own child, while most males are infertile. These are all significant issues that impact many of us with CF on a daily basis. I remember on October 16, 2017 I was a full-time high school teacher, department chair, and involved in many committees within my building. Less than 24 hours later I became severely ill and was hospitalized. My initial thought was, "hey, I need to be out by Friday morning, I'm a bridesmaid in my friend's wedding, give me some IV antibiotics and let me get back to my job, my house, my dogs, my life". I originally started out on the hospital floor that dealt with CF patients, but within a couple of days had to be transferred to ICU in respiratory failure, I wasn't going to go to the wedding or back to work for a couple of weeks at least.

In ICU I was placed on a vapotherm to help me breath and ended up with sepsis from a port placement. The port that I had so much put off for so long had become an easier way for me to do IV antibiotics instead of continuing to have PICC lines placed since many of my veins were starting to reject the lines. Due to the sepsis the port had to be removed and I had to

resort to PICC lines again. I was in the hospital for three weeks, although my doctors pushed for me to stay much longer. I have always been compliant so I kept pitching to them that if I can do my treatments, pulmonary rehab, oxygen, etc. that I would be more comfortable within my own home. After all I had a husband and family that was willing to put forth the effort to care for me.

Much to the doctors' hesitations I went home on IV antibiotics and drugs that had been flown in from other areas of the country. I still was unable to dress, feed, bathe, or walk on my own. I required 24/7 care from those around me. I couldn't walk to the bathroom, I couldn't make it from the couch to the kitchen table, I slept almost constantly between treatments and IV antibiotics, but I was happier. I was in my own home, sleeping in my own bed, eating my own food, and snuggling with my dogs on the couch. Slowly over multiple weeks I could start to stand without help, I could move a little faster, and I was starting to require less continuous oxygen. It was a long road over five months to get to where I am today.

I thought that after this I was going to go back to work, that day never came and it never will for me anymore. I was constantly sick and on meds every few weeks due to exposure and my doctors decided that this was it, it was time for me to give up what I loved, my purpose in life. It was a hard pill to swallow as I started to think about what my future was going to be like not working and going on disability. I became more worried about my future and what further lung deterioration meant for me.

I had to look at life from a new perspective, if I considered nothing else except my CF what made sense? It was after all to quit working and find a new purpose in life at home. I put on a brave face and faced that challenge and I ended up seeing a reward at the end of the tunnel-I was no longer sick all the time and as hard as that was to leave behind my career, it was after all the best choice I could make for myself and for those that love me.

I am forever grateful to my ICU doctor and credit him for saving my life. Without him providing me the best possible care, I truly believe I wouldn't be here. I now spend my days as a mentor for the CF Foundation and caring for my three dogs, without them I would be lost. I truly believe that pets can have a significant impact on our mental and emotional health in its own way. My husband also sees the benefits, I appear healthier, I cough less, perform household duties more on my own.

While I still feel the significant impacts of my disease, and with no current CF modulators available for my mutations, I have hope. I know that I must stay in the best health as possible for when those advancements become available. With the help of the FDA all patients living with CF will someday have life-saving treatments, and hopefully someday a cure.

I'd like to thank the FDA for being a part of this fight and listening to our community voice and to all those manufactures that are fighting night and day to make a treatment available to help all patients with CF fight another day. In summary I just want the FDA to know how much this disease impacts every part of my body and my life. My life, and my families, revolves around having CF.

The recent advancement of the Monarch machine has made it possible to tailor a small part of my life to not always having to come home for treatments. I have done IV antibiotics with the help of a portable IV machine and the monarch vest while sitting in a tree stand hunting, I can go on our pontoon and be able to do a treatment in the middle of the lake. All of these small things have made a significant impact on my life. I have great hope that more life changing advancements will be able to alter how I live my life.
Thank you!
Jessica
From Wisconsin

From: Jessica L., adult with CF
Re: Reproductive Health

In Wisconsin it costs around $50K to adopt domestically and that doesn't take into account that individuals with CF may be "red flagged" or denied based upon our diagnosis. That was the information my husband and I were told a couple years ago because to the agencies "life threatening" means they're putting a child into a home where they may lose a parent at a young age and deal with more emotional struggles and only have one parent left to care for them. Surrogacy in WI is an excluded insurance coverage even if medically necessary and the costs on one's own range from 120-200K with no guarantee. That's a large sum on money that many CF patients can't afford due to the high costs we pay toward insurance coverages and once someone is on disability would make it even more difficult not having the type of money coming in

that once did when working. Just food for thought.
Thanks for your time,
Jess

From: Somer L., adult with CF
Re: New Therapies

When new drugs become available for Cystic Fibrosis I can't help but have a glimmer of hope. For the first time in a long time having hope feels like a breath of fresh air, but also is so scary and nerve racking. It is an exciting time in the CF community, but living with lung function that hovers around 27% and living on full time oxygen I can't help but feel like I need to air on the side of caution. I literally think about every breath I take.

A typical day for me consists of hours of breathing treatments, airway clearance, exercise, handfuls of pills, sterilizing neb cups, and a healthy diet and this is all just the regular maintenance for when I am healthy, I work so hard day in and day out just to be able to breathe. CF is not easy, it is inconvenient, and it can be very exhausting. Time is of the essence for all of us with CF especially, those of us with end stage lung disease. Although I often remind myself that I have 39 years of damage to combat with the drugs that I am currently taking, that glimmer of hope still remains that soon one day there will be more options to help me breathe just a little easier.
Breathe out Love,
Somer Love, LoveToBreathe.com

From: Angela K., mom of two adults with CF
Re: Mental Health

Regarding weight control issues, another interesting, and perhaps surprising to some, factor that can play a huge role with teens and young women in particular is body image issues. With my 20-year-old daughter, she can get overly obsessed with wanting to maintain her slim physique against the physician's desire for her to gain weight. There is an ironic twist to the way weight control issues can impact the life of a young woman struggling with wanting to protect her health vs her desire to maintain an image that ends up being very prominent to her. With the modulator treatments helping patients to gain weight, this may be something of a struggle that we start to see more of in the future.

From: Megan N., mom of child with CF
Re: Mental Health

By age 3, my son was cursing out CF and we could be longer get him in the car for procedures. He's 14 now and has had 40 surgeries...24 sinus surgeries, 10 PICC lines, 2 port surgeries and others. It's a disaster. He was diagnosed with PTSD and became a medical marijuana patient of NJ two years ago. He uses this for severe GI pain and anxiety relief before surgeries. It's been the only thing that works for times like this. I don't get how doctors are comfortable prescribing Percocet and Morphine for his pain but nobody offers Information about the much less addictive marijuana. It should be looked at for certain circumstances without the stigma that it currently has. Aidan is doing much better since starting Symdeko and we are forever grateful...he is actually the cover boy for the drug :) That has to be a good sign!

From Jennifer K., adult with CF
Re: Chronic Pain, Fatigue, Social Activities, Sinus, Gastrointestinal Symptoms

I deal with early onset arthritis, pancreatic insufficiency and sinus infections. Each day I deal with pain just on differing levels. This is extremely tiring. If I have plans to go out at night, I have to make sure I get at least an hour nap so I can get through the social outing.

From Jennifer K., adult with CF
Re: Medicare, Spousal Coverage

Since getting divorced 2 years ago and losing my husband's insurance, Medicare has become my primary coverage. I was taking Pulmozyme twice a day under my husband's coverage. Medicare has put me on a half dose so now I take hypertonic saline in its place. I miss how good I felt on the 2x/day Pulmozyme. The saline helps a lot but for me the Pulmozyme was better. We need to get better regulations so as patients we can get the meds we need at the doses that work for us.

Topic 2: Perspectives on Current Approaches to Treating CF; Goals for Potential Treatments; Drug Development Issues/Clinical Trials

From: Laura F., parent of adult with CF and pediatrician
Re: Lung Exacerbations, Death, Maintaining Financial Stability, Clinical Trials and Assumption of Risk

I am writing to you because I was unable to attend the externally led patient focused drug development meeting on cystic fibrosis and would like to add my voice. I am a full-time pediatrician and parent to a 22-year old young (old) man with cystic fibrosis.

I would like to add a few observations and personal preferences that may differ from what has already been mentioned. First, I must emphasize to you that cystic fibrosis is a progressive, universally fatal disease. You will forgive me for stating the obvious, but I believe that the progressive nature of the disease is often overlooked and forgotten. Dr. Uluer, who so eloquently reviewed many of the negative multi-organ effects of cystic fibrosis, noted that adolescents with CF have a drop in lung function and he attributed this drop to a decrease in patient adherence. I was disappointed with his overly simplistic explanation. I must emphasize to you that cystic fibrosis is a complex, progressive disorder and that even with maxmum optimization of current management, universally leads to enormous morbidity and early death. I do not dispute that patient adherence effects outcomes, but I believe the culture in the CF community of "blaming the victim" is an unintended consequence of making the registry outcome data public in 2006. Physicians have felt a need to rationalize and have minimized their own role in variability of care provided at different centers.

I would also like to discuss cystic fibrosis life expectancy. Unlike with other diseases where median life expectancy is quoted, in most of the cystic fibrosis literature, median predicted life expectancy for someone born today is referenced. While the median life expectancy is <30 years overall for the entire CF population, what is the life expectancy for patients who have the severe double delta mutation like my son's? Is it 27 years? Is it 24 years? Of note, one-half of the cystic fibrosis population has "severe" mutations, and for this population, the current median life expectancy is not published. Obviously as the FDA is trying to balance the risks and benefits of new treatments, you must have as clear a picture as possible about the severity of the disease. This information could be readily available from the national cystic fibrosis registry; however, it is not published.

My son has had many of the complications already mentioned in the meeting: meconium ileus surgery, 28 courses of intravenous antibiotics, multiple PICC lines, broviac, port-a-cath, many line complications, chronic colonization with MRSA, NTM infection, etc. In addition, he has had the added, not previously mentioned, complications of a severe, steroid-dependent reactive arthritis, which often left him completely un-ambulatory and lasted 7 years. He has also had recurrent kidney stones and lithotripsy. I will not describe the emotional impact of this disease or the intense daily treatment burden, even when people with cystic fibrosis are not "ill", as others in the community have already done so.

Despite the enormous impact of his illness on my entire family, and the multiple indicators of severe disease, one could not guess that my son could continue to maintain normal lung function; he is categorized as having "mild" lung disease, certainly not as "disabled." Yet, when he decided to become a pilot, after completing his training, the Federal Aviation Administration clearly discriminated against him, and based on his diagnosis alone, without regard to his current ability, denied him a pilot's license, even for a solo craft. When my son started working full time at his next job, his health suffered and he had to quit and has since gone back to online school. Last year, he was on intravenous antibiotics for a total of 4 months. The treatment burden with this disease is so high that in order to adequately manage one's health, working full time is not really an option for most. People do it, but there is a price to pay. So, even with "mild" lung disease, is he disabled? Will he be able to find a part-time job that also provides benefits?

Unfortunately, a culture exists whereby patient advocates are categorized as having "therapeutic misconception" where they confuse the knowledge-seeking mission of research with the patient centered mission of medicine, thus, making it difficult for patients to adequately assess risks and benefits of potential new therapies. I suggest that the opposite is true. Clinicians and researchers are driven by their desire, first and foremost, to "do no harm." I believe that physician scientists therefore can more readily accept the negative consequences of the natural course of a disease rather than the potential complications resulting from an active intervention.

And so I come back to my son, with normal lung function but severe cystic fibrosis, who coughs constantly, who regularly makes a guttural noise to bring up sputum, who doesn't know what it's like to take in a full breath of air, who

is often misunderstood, who has learned to live with disappointment and the unexpected, and who doesn't know if he has any kind of a future. And so despite his normal lung function, we are willing to accept risk, not because of some kind of "therapeutic misconception," but because as highly educated and informed patients, we can be more objective than investigators. We can more readily accept many potential adverse outcomes of new therapies, rather than accept the inevitable natural course of his disease.

The most important outcome that we seek is halting the progression of his disease. Many in the CF community asked for the gift of time because they don't want additional therapies developed that could add to the already heavy treatment burden. However, I view this wish as the "cherry on top." Certainly having more time in the day would be fabulous for my son but I must emphasize that halting progression of disease is much more important. So, it isn't improvements in FEV1 that we seek, it's changing the slope of lung function decline.

In addition, other outcome measures from new therapies would hopefully decrease pulmonary exacerbations. Are we able to keep NTM from recurring, an organism which has been shown to double the rate of decline? Can we prevent new infections or at least readily eradicate them? Can we find better markers for disease other than lung function? Will his CT scan remain stable or even improve after a new treatment? Will he tell me he can suddenly breathe better? Will he tell me he feels good? Will he have less cough? Will he have a change in the frequency of this guttural noise when he brings up sputum? Will he notice a clinical difference? Will he feel good running? Will he wheeze less? These are some of the outcomes we seek.

And yes, we would accept risk despite having normal lung function. In fact, my son would have participated in CFTR modulator trials had he met the inclusion criteria. I believe the inclusion criteria for cystic fibrosis trials should not be limited to certain lung functions or certain microbiology colonization. I worry about insurance companies using any excuse to exclude patients from drug coverage after FDA approval of new therapies.

When it comes to cystic fibrosis care, I believe there is tremendous implicit bias because patients look normal, particularly when they have normal lung function. Evidence from the patient registry, for example, shows that physicians are less likely to treat and prevent irreversible damage in patients with mild disease. When balancing risk and benefit, it is important not to underestimate the severity and suffering that results from this relentless disease and to understand that lung function does not paint the whole picture. It is also important for the FDA and researchers not to underestimate the ability for educated patients to understand the risks and benefits of potential new therapies. Managing this disease is exhausting; I don't know how much longer we can hold on to this lung function. We need new therapies NOW! I am saddened that Vertex is testing 2 different triple combo CFTR modulators, rather than proceeding with one of them and submitting sooner to the FDA for approval.
Thank you for giving me the opportunity to voice my opinion.
Sincerely,
Laura F., MD FAAP

From: Melissa S., adult with CF
Re: Clinical Trials

I did not participate in clinical trials until I was older. I knew I wanted to have children and my doctor and I discussed our mutual concern that a trial may have a negative effect that would impact my ability to get pregnant and stay healthy. Once my kids were out of the toddler stage, I eagerly waited to get on a CFTR trial for my mutations. I finally got to participate in the trial for Symdeko which did feel like the lottery. What I did not realize until the day I started was how vulnerable I felt. I was so focused on being able to try something that could have a profound effect on my health (it didn't) that until they drew the first blood and handed me the pill, I did not think about the possibility of a negative outcome. That being said, I would do it again in a heartbeat. The drug has not improved my FEV1 as I'd hoped but it has helped so many. I should add that during the trial, when it was time for the first washout, I got severely sick and had to go on IVs and postpone the 2nd half of the study.

From: Jeannine R., adult with CF
Re: Lung Exacerbations, N-of 1 Clinical Trials

Thank you for organizing the FDA meeting. I'm sure it was a massive undertaking and the time and effort you put into was obvious. I have some thoughts that I didn't have time to pass along during the event. Hopefully, it's not too late and you're

able to add this information to the comments made on Monday. I'm a CF patient and have the R334W and F508del mutations. For the past 4 years, I've had the privilege of taking Kalydeco off-label with very positive results. I wrote an article that explains my experience and my plight to help others gain access to this breakthrough drug. Unfortunately, those with R334W have not been included in Vertex trials, despite it being one of the more common mutations and despite the fact that most with this mutation (60%) are pancreatic sufficient, which suggests that they have some CFTR protein at the cell surface that could possibly be potentiated by Kalydeco. There are 407 people with my missense mutation, many of whom don't have F508del and won't benefit from Vertex's triple combo that is in the pipeline. According to the CFTR2 database, there are 177 people with R334W and a mutation other than F508del on their other allele. These 177 people are being left behind, without any chance to participate in a clinical trial to evaluate CFTR modulators that theoretically should provide an effective treatment, one that may be life-altering and life-saving. I would like to share my story with the hope that it will be considered as the FDA decides how best to conduct clinical trials that support personalized medicine in rare diseases, such as Cystic Fibrosis.

In 2010, my CF progression started to accelerate. My quality of life began to deteriorate and IV antibiotic use became more frequent. In 2014, my lung function was in the 30's; I suffered from frequent coughing fits, constant wheezing, shortness of breath with activities, persistent joint pain, low-grade fevers, fatigue, and hemoptysis. My sputum started to become more resistant and I was not responding to IV antibiotics. I was headed toward the path of needing a lung transplant. In November of 2014, I was fortunate enough to have the opportunity to try Kalydeco off-label. Within days of starting, I could tell that Kalydeco was working. My wheezing and chest tightness improved dramatically. Within 5 days of starting, my lung function (FEV1) went from 31% to 41%.

All of my symptoms were improved:

- *I was able to sleep through the night without the coughing fits that had plagued my sleep for years.*
- *My cough, wheezing, and sputum production were greatly reduced*
- *Hemoptysis improved*
- *Increased exercise tolerance*
- *Fatigue, fever, and joint pain greatly reduced*
- *My oxygen saturation improved at rest and with exercise.*

All of these improvements have been sustained for 4 years. Since starting Kalydeco in 2014, I've only required IV antibiotics once. For the few years leading up to Kalydeco, I was averaging IV antibiotic use 2-3x/year. I have no doubt that Kalydeco has slowed down my disease progression. It is not a cure by any means and CF still remains very present in my everyday life. My treatments continue and I still have symptoms; however, these symptoms have been significantly mitigated. Fear for my future is no longer the first and last thought of my day. Kalydeco has undeniably added years to my life. If my stability continues on this path, Kalydeco may prevent the need for me to receive a lung transplant in the future.

Please consider N-of-1 studies as a valid option for a clinical trial. I don't see any other way that people with rare mutations (or not so rare as is the case with R334W) will gain access to these groundbreaking treatments. It's simply unacceptable not to give them the opportunity to try a potentially life-altering drug with a very sound safety profile. By doing so, they are being discriminated against because of the rarity of their genetic make-up. I will follow-up this e-mail with 2 published abstracts providing proof that CFTR modulators enhance the function of the R334W mutation. I also will include an article, which "provides the first evidence that correction of CFTR function in HNE cell cultures can predict respiratory improvement by CFTR modulators."

Thank you for giving CF patients a voice and listening to our concerns and our stories. We are a resilient and compassionate group that won't give up this fight until every person with CF has a highly effective treatment, or better yet, a one-time cure.
Sincerely,
Jeannine R.

From: Anna M., adult with CF, 37 years old
Re: Cannabis for Weight Gain

One of the parents in the last roundtable spoke of appetite stimulants. I would like to explain how stimulants have help me achieve a BMI>18% There are only three approved drugs to stimulate appetite. I've taken all three at times. Oxadrin did not work for me and I also do not like taking hormones. Megase, another steroid, cause an unwanted side effect of making

my hair fall out. My current insurance company would not approve Marinol so I was forced to either pay out of pocket or get assistance from the manufacturer. I was approved for assistance from the manufacturer, so I get my drug at no charge. But that is to say not every patient will be approved and there is a long waiting period.

Marinol has a negative connotation associated with it due to it being a synthetic cannabinoid. Seeing that marijuana is legal in several states for both medical and recreation use, the FDA needs to relabel the use of Marinol in patients with CF, as well as, other such conditions as bulimia and anorexia. The drug has been a lifesaver for me. It is unacceptable that insurance will not approve an appetite stimulant for anyone other than a cancer patient. To be listed on the lung transplant list, most centers requires a BMI above 18%. CF patients have a hard time keeping weight on energy is "wasted" on such things as coughing, exercise that is encourages, breathing and a higher resting heart rate than their peers at the same age and weight. I'd like the FDA to consider not only approving Marinol for use in CF patients, but also to consider other edibles that contain cannabis to stimulate appetite and decrease pain. Currently, it is on the state to regulate these laws which is find unacceptable when it may be a lifesaving measure for my disease.

From: Annie C., adult with CF
Re: Maintaining Financial Stability, Off-Label Insurance Coverage, Rare Mutations

I am listening to the meeting and wanted to send in my comment/question in advance since I am at work today and I'll be in and out. I have DF508 + a rare missense mutation (L1335P) that confers some residual CFTR function - about 2.5%. L1335P has not been studied at all by Vertex and it has not been included in any modulator trials. I began taking Kalydeco off-label in 2014 and Symdeko off-label in 2018. My sweat chloride has decreased, lung function increased, weight gain, way less coughing and mucus, etc. Symdeko especially has been a huge boost in my quality of life. But, relying on off-label insurance coverage is stressful, precarious, and burdensome.

My questions are about cases like mine of rare mutations that may be responsive to existing CFTR modulators but are not on-label. (This is not a question about people with nonsense mutations that aren't responsive at all to CFTR modulators - this is a separate issue.)

1) *Is there any systemic effort to track all patients using CFTR modulators off-label and what their results are?*
2) *How was the decision made to include some residual function mutations for the expanded label for Kalydeco and Symdeko? Was there a specific threshold used as far as how much residual function the mutation had to have? There was a lack of transparency about why some mutations were chosen and not others.*
3) *Is there any way patients can advocate to the FDA for inclusion of their mutations in CFTR modulator labeling, or for their mutations to at least be included in studies?*
4) *For the upcoming Vertex triple combo: My understanding is that it is expected to work for DF508 + anything. However, trials are being done only on DF508 homozygotes and DF508+ minimal function. How do you anticipate the triple combo will be labeled? What about DF508+gating or DF508+residual function? What about DF508+a mutation that hasn't been clearly categorized as any of these things? My fear for people like myself (DF508+a rare non-studied mutation) is that we will not be "on label" for a very long time. As patients with rare mutations that may be responsive to CFTR modulators, we need more transparency about how decisions are being made to include or exclude us from trials and drug labeling, and what the timeline looks like for us to get "on label" in the future.*

Thank you!
Anna C. (New York, NY)

From: Jeannine R., adult with CF
Re: Clinical Trials

First I want to thank you for organizing this extraordinary opportunity. Your efforts to bring this massive undertaking into fruition are greatly appreciated. It's imperative that the patient voice is heard.

Unfortunately, due to schedule conflicts, I'm not able to watch the event in its entirety. I have watched the morning session and participated in the polling. I did have a question relating to Dr. Uluer's presentation.

In Dr. Uluer's presentation he mentions 2 ways to access therapies outside a clinical trial:

1. Right to Try

2. Compassionate Use

Access to drugs following completion of Phase 3 clinical trial and before FDA approval.

My question is: Is it possible for drug companies to include an expanded access program (compassionate use) during the Phase 3 clinical trials? This would allow people not eligible for clinical trials (perhaps because they have an FEV1 of below 40%) to have access to an investigational drug that shows clear promise? As shown in his previous slides, the therapeutic results for the Phase 2 triple combo studies were phenomenal and most adverse effects were mild to moderate in severity. During my research of this subject, I've found that from the FDA's standpoint, it's possible to offer expanded access programs during Phase 3 trials, not just following the completion of Phase 3 clinical trials and before FDA approval as Dr. Uluer's slide suggests. It appears to be the choice of the pharmaceutical company whether they decide to offer expanded access during Phase 3 (and some pharmaceutical companies even have included EAPs during Phase 2 trials.) Can you please clarify this? Am I correct in my interpretation of the FDA guidelines for the use of expanded access programs that would allow for expanded access during a Phase 3 trial? Would there be any point during today's presentation that an issue such as expanded access would be discussed?
Thank you,
Jeannine R.

From: Robert O., father of child with CF
Re: Lung Exacerbations, Increasing threat of NTM and MDR in CF

Why is this happening? What resources are being thrown at this topic? What is the FDA and researchers doing to enhance a drug pipeline in this direction? We seem to need more incentives for anti-infective drug development

From: Somer L., adult with CF
Re: New Therapies

With new drugs I would love for CF not define me. You never want CF to define you, but from the moment I wake up to the second I go to bed CF is on the forefront of my mind. As my disease progresses and being on full time oxygen I would say CF does define me, it is very limiting as it progresses. I have to make new normals, as I continue to make adjustments to my life with every decline. Stability is key and I hope that at the very least with new medications I can have stability.
Breathe out Love,
Somer Love
LoveToBreathe.com

As CFRI celebrates 43 years of research and service to the cystic fibrosis community, we thank and honor all those who have supported our efforts to extend and enhance the lives of those with CF. CFRI provides a range of services to meet the multi-faceted needs of our CF community.

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CF Caregivers Support Group

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CF Summer Retreat

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1731 Embarcadero Road, Suite 210, Palo Alto, California 94303 USA
Toll Free 1.855.cfri.now (1.855.237.4669) **www.cfri.org**