The Final 10%

A follow-up survey to understand the perspectives, unmet needs, and clinical research preferences of the 10% of people with cystic fibrosis not benefiting from CFTR modulators

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EMILY'S ENTOURAGE

About the Survey

Emily's Entourage (EE) is pleased to share the results of the 2022 "Final 10% Survey" Report. The report contains a summary of survey responses from individuals that are part of the final 10% of the cystic fibrosis (CF) population that do not benefit from currently approved cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies due to ineligible genetic mutations, therapy-related side effects, suboptimal response, and/or lack of access.

This survey was designed to collect information from people with CF (pwCF) over the age of 18 and the family members and legal guardians of pwCF on how the disease affects their lives, what concerns them about the disease, their opinions on current and potential treatment options, their experiences with and perspectives on research studies and clinical trials, and the difficulties they face as members of the a small group that does not benefit from modulator therapy.

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Survey Results Overview

This report summarizes the survey responses and comments provided by pwCF and caregivers in the 2022 "Final 10% Survey." As much as possible, we have incorporated pwCF's and caregivers' own words, so as to represent their views as accurately as possible. The main themes from the survey are as follows:

- The majority of pwCF and family members of pwCF who completed the survey reported ineligibility for a CFTR modulator (58.0% pwCF, 71.3% of family members of pwCF).
- Most frequently reported symptoms and signs reported by pwCF included excessive cough (70.0%), fatigue (61.4%), pulmonary exacerbation and chronic lung infections (55.0%), shortness of breath (54.2%), and sinus disease (52.0%).
- Among pwCF, 39.4% reported their mental health status was "fair" or "poor." Among family members of pwCF, 50.8% reported their mental health status as "fair" or "poor."
- The disease has an enormous effect on treatment burden with 70.4% of pwCF spending 1–4 hours a day on treatments.
- pwCF expressed that while a cure for the disease as a whole is needed, treatments that improve lung function (76.0%) and address lung infections and exacerbations (59.0%) are the most important aspects of CF for new therapies to address.
- pwCF reported that CF had a significant impact on their lives with the areas most impacted including plans for the future, daily life in general, staying healthy for your dependents, travel, mental health, finances, family planning, ability to spend time with friends/participation in social activities, participation in sports, hobbies, or extracurricular activities, and work or employment issues (i.e. finding and keeping a job).
- Among pwCF, 50.3% had participated in a clinical trial before and 83.0% expressed interest in participating in a future clinical trial. The main motivations for enrolling in a CF clinical trial were the possibility of improving their own health (89.7%), the desire to help find a cure (87.3%), the desire to help the CF community even without personal benefit (66.0%) and to have free access to new study drugs (58.7%).

Introduction

Cystic fibrosis (CF) is a progressive, multiorgan genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It can occur in people of any race or ethnicity. The advent of highly effective CFTR modulators has significantly improved quality of life and long-term prognosis for individuals in high-income countries (HIC) who benefit from and have access to approved CFTR modulators. Despite the advances, approximately 10% of people with CF (pwCF) still have no access to treatments that address the basic cause of CF due to ineligible genetic mutations, therapy-related side effects, suboptimal responses, and/or lack of access based on where they live.

On June 10, 2022, Emily's Entourage (EE) launched the 2022 " Final 10% Survey" of the CF community, incorporating feedback from a multitude of stakeholders, including CF Foundation's Community Voice, Cystic Fibrosis Research Institute, pwCF and family members of pwCF, and an independent contractor specializing in survey methods and data analysis. Although patient registries have been instrumental in collecting data and describing clinical characteristics of pwCF not benefitting from modulator therapy, they do not capture the burden of care pwCF and their family members endure on a daily basis, nor their experience of and views on symptoms, treatments, and participation in clinical trials. The goal of the survey was to give pwCF who are not eligible, do not have access to, or are unable to take and tolerate CFTR modulator therapy and their family members a forum to discuss their perspectives on their condition, available therapies to treat their disease, experiences with and interest in research studies and clinical trials, and their hopes for future treatments and a cure.

Overview of Cystic Fibrosis

Mutations in the CFTR gene are the primary cause of CF, a hereditary condition that can affect persons of any race or ethnicity. Clinical manifestations of CFTR protein malfunction typically include decreased mucus clearance, leading to chronic lung infections, pancreatic insufficiency, diabetes, and infertility amongst other complications.

Treatment options for pwCF have undergone significant development in the past ten years; medications have been developed that treat the fundamental problem that causes CF. This group of medications, called CFTR modulators, enhances the transport and activity of the CFTR protein, resulting in substantial improvement in lung function, weight, and quality of life. Approximately 90% of the CF population has a mutation that is expected to benefit from CFTR modulators.

While the development and approval of CFTR modulators have significantly improved daily life and prognosis for the majority of pwCF in HIC, approximately 10% of pwCF still do not have any therapies to treat the underlying cause of CF. Black, Indigenous, and People of Color (BIPOC) are disproportionately prevalent in this group of pwCF due to their understudied and/or rare mutations. There are also pwCF who are eligible to take these modulators based on their mutations, but are unable to do so due to side effects. Lastly, many countries lack the means to provide their citizens with a CF diagnosis and access to CFTR modulators, resulting in significant global health inequity. There is no cure for CF.

Survey Development

The survey consisted of 72 questions that were formulated by EE staff with suggestions from various stakeholders, including CF Foundation's Community Voice staff and Jennifer Taylor-Cousar, MD, MSCS, ATSF.

The survey also incorporated feedback collected during an open submission period between April 5 and April 19, 2022, during which all members of the CF community, including pwCF, families of pwCF, clinicians, researchers, regulators, and biopharmaceutical companies, could submit suggested questions or topics for the 2022 survey. The format of survey questions included multiple choice, Likert type scales, and free text responses. The survey was conducted in English.

The survey was adapted from the 2021 " Final 10% Survey" conducted by EE, which consisted of 38 questions. The 2021 survey generated 431 responses from pwCF on five continents. The results were published in *Pediatric Pulmonology* in May 2022. The 2022 "The Final 10%" survey was conducted between June 10 and August 25, 2022. It was shared on social media channels, including Twitter, Facebook, Instagram, and LinkedIn, and by email to pwCF, their families, and advocacy organizations around the world, including in the United States (US) and territories, Canada, United Kingdom (UK), Australia, and Israel. The organizations were then asked to share the survey with other relevant individuals and groups. Additionally, EE distributed the survey to its CF nonsense mutation patient registry, a global registry of people with at least one nonsense mutation of CF. The survey was closed on August 25, 2022.

Survey Results

Survey respondents and their relationship to CF

The majority of people who responded to the survey were adults with CF (n=187/313, 59.7%). The other respondents included parents of children ≤17 years of age (n=31/313, 9.9%), parents of adult children over the age of 18 years old (n=77/313, 24.6%), spouses/partners of a person with CF (n=11/313, 3.5%), and other family members including a grandmother, a cousin, two siblings, and a grandson. pwCF or their family members hailed from 39 states within the US (including Puerto Rico) and 28 countries outside the US, with Israel, UK, Australia, and Brazil having the most representation. **(Table1)**

Demographics of survey respondents

More women responded to the survey (64.0%) than men (32.4%). Most respondents reported their race as white (83.0%) and not Hispanic or Latinx (6.1%).

Among pwCF and family members of pwCF, 58.0% of respondents reported living in the US and 42.0% reported living outside the US on five continents: Africa, Asia, Australia, Europe, and South America. Respondents were concentrated in the following countries: Israel (27), UK and Ireland (23), Australia/New Zealand (18), Brazil (14), and Canada (11). Within the US and territories, participants came from 39 different states with 28 participants from California, 16 from New York, and 16 from Pennsylvania.

Among pwCF, private insurance coverage was most common (51.4%) followed by medicare (37.1%) and medicaid (18.1%).

TABLE 1. Demographics of people with CF described in the survey

	Adults with CF		Family members of pwCF		Total	
Overall respondents	**n=187***		**n=126**		**n=313**	
Gender identity	**n=149**		**n=98**		**n=247**	
Woman	102	68.5%	57	58.2%	159	64.4%
Man	40	26.9%	43	43.9%	84	34.0%
Gender non-binary or genderqueer	7	4.7%	0	0%	7	2.8%
Prefer not to answer	1	0.7%	0	0%	1	0.4%
Race**	**n=148**		**n=99**		**n=247**	
White	121	81.8%	84	84.9%	205	83.0%
Middle Eastern or North African	10	6.8%	1	1.0%	11	4.5%
Hispanic or Latinx	6	4.1%	9	9.1%	15	6.1%
African American or Black	3	2.0%	4	4.0%	7	2.8%
Southeast Asian	3	2.0%	1	1.0%	4	1.6%
African or Afro Caribbean	2	1.4%	0	0.0%	2	0.8%
Native American	2	1.4%	2	2.0%	4	1.6%
South Asian	2	1.4%	3	3.0%	5	2.0%
East Asian	1	0.7%	0	0.0%	1	0.4%
Alaskan Native	0	0.0%	0	0.0%	0	0.0%
Native Hawaiian or Pacific Islander	0	0.0%	1	1.0%	1	0.4%
Not listed	8	5.4%	7	7.1%	15	6.1%
Prefer not to answer	4	2.7%	0	0%	4	1.6%
Country of residence	**n=185**		**n=122**		**n=307**	
US	107	57.8%	71	58.2%	178	58.0%
Outside the US****	78	42.2%	51	41.8%	129	42.0%
Insurance	**n=105**		**n=70**		**n=175**	
Private insurance (employer)	54	51.4%	55	78.6%	109	62.3%
Medicare	39	37.1%	7	10.0%	46	26.3%
Medicaid	19	18.1%	17	24.3%	36	20.6%
Private insurance (self-pay)	10	9.5%	4	5.7%	14	8.0%
State special needs program (e.g., BCMH, CCS, CRS, GHPP)	8	7.6%	2	2.9%	10	5.7%
No insurance	8	7.6%	1	1.4%	9	5.1%
Military health care (e.g., Tricare/VA/CHAMP-VA)	4	3.8%	1	1.4%	5	2.9%
Distance from CF Center	**n=182**		**n=120**		**n=302**	
≤30 minutes	43	23.6%	39	32.5%	82	27.2%
30–59 minutes	61	33.5%	43	35.8%	104	34.4%
1–2 hours	53	29.1%	21	17.5%	74	24.5%
>2 hours	19	10.4%	14	11.7%	33	10.9%
Don't have a care center	4	2.2%	0	0%	4	1.3%

* Based on participant choice and question composition, the number of respondents (n) for each question varied; for demographic questions, with the exception of age, participants were not limited to one choice (e.g. the number of responses may exceed the number of respondents).

** Because race and ethnicity are social constructs, their definitions vary by country.

Clinical characteristics

CF is a multisystemic progressive disease with significant variability in the severity of manifestations between pwCF. Forced expiratory volume in 1 second (FEV1) is a measure of how much air can be emptied from the lungs in the first second of forcefully exhaling and is a useful indicator of lung health and disease progression. Among pwCF, 16.4% had mild lung disease (baseline ppFEV1 ≥ 90%), 58.2% had moderate lung disease (ppFEV1 40%–89%), and 22.0% had severe disease (ppFEV1 < 40%). Among family members of pwCF, 34.8% had mild lung disease (baseline ppFEV1 ≥ 90%), 42.4% had moderate lung disease (ppFEV1 40%–89%), and 5.1% had severe disease (ppFEV1 < 40%). **(Figure 1)**

The majority of respondents reported experiencing symptoms of pulmonary exacerbations and infections on a regular basis (54.8%) with the most common pathogens being *Pseudomonas aeruginosa* (58.3%), *Staphylococcus aureus* (30.4%), methicillin resistant *Staphylococcus aureus* (MRSA) (13.1%), and multidrug-resistant *Pseudomonas aeruginosa* (12.5%). **(Table 2)**

FIGURE 1. What is your/your family member's baseline FEV1?

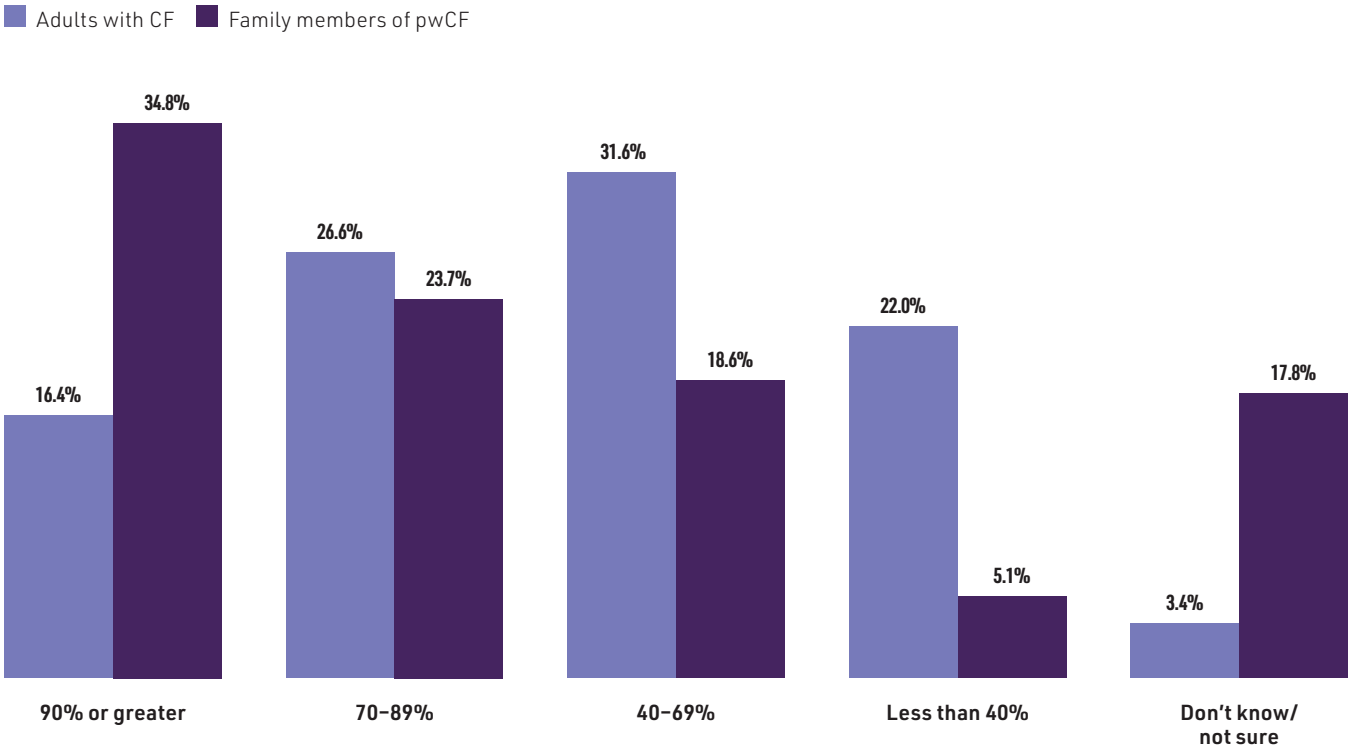


TABLE 2. Which respiratory pathogens do you /does your family member currently grow in sputum cultures?

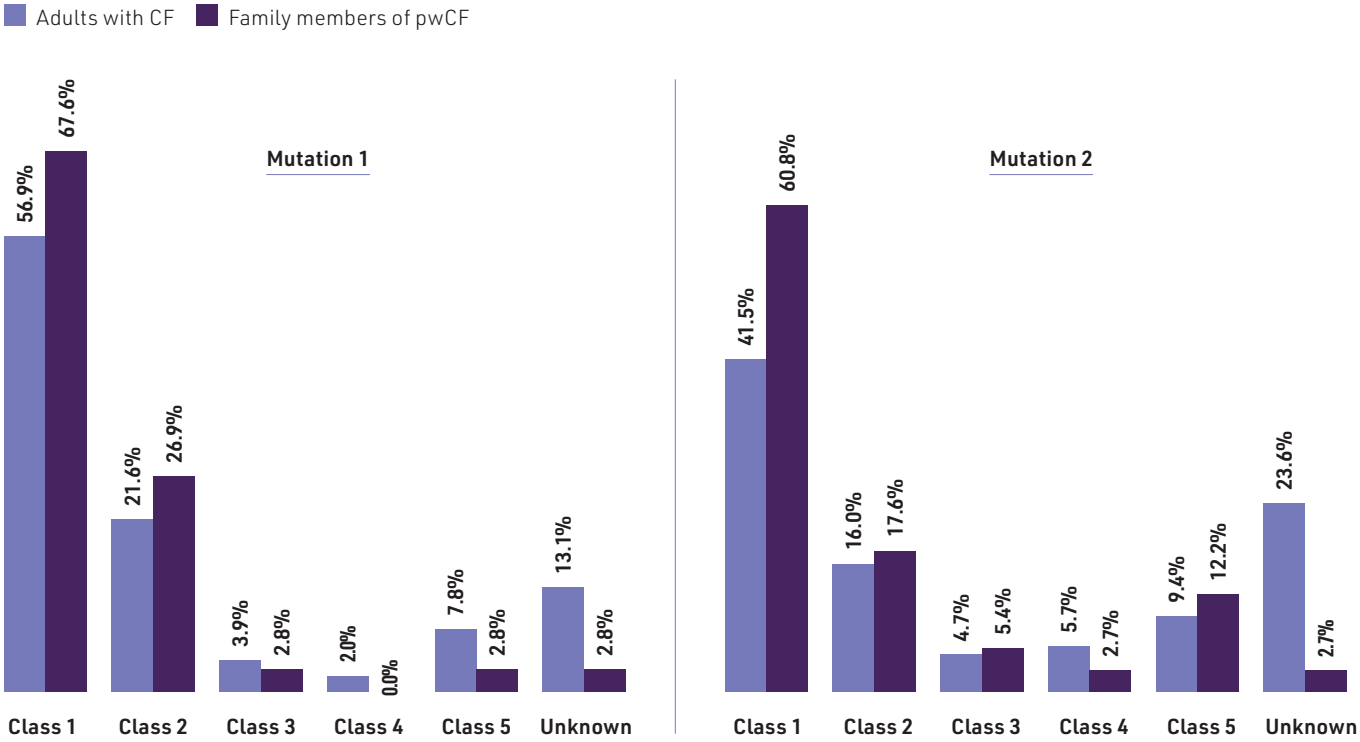
	Adults with CF		Family members of pwCF		Total	
	n=168		n=108		n=276	
Pseudomonas aeruginosa	98	58.3%	41	38.0%	139	50.4%
Staphylococcus aureus (staph)	51	30.4%	42	38.9%	93	33.7%
Aspergillus	28	16.7%	23	21.3%	51	18.5%
Methicillin-resistant staphylococcus aureus (MRSA)	22	13.1%	15	13.9%	37	13.4%
Multidrug-resistant pseudomonas aeruginosa (MDR-PA)	21	12.5%	4	3.7%	25	9.1%
Nontuberculous mycobacteria (i.e., M. avium complex/MAC, M. abscessus)	16	9.5%	8	7.4%	24	8.7%
Methicillin-sensitive staphylococcus aureus (MSSA)	13	7.7%	10	9.3%	23	8.3%
Stenotrophomonas maltophilia (S. maltophilia)	13	7.7%	10	9.3%	23	8.3%
Achromobacter	10	6.0%	7	6.5%	17	6.2%
Haemophilus influenzae	4	2.4%	12	11.1%	16	5.8%
Burkholderia cepacia complex (B. cepacia)	10	6.0%	5	4.6%	15	5.4%
Don't know/not sure	8	4.8%	9	8.3%	17	6.2%
Other (please specify)	14	8.3%	8	7.4%	22	8.0%
No growth	18	10.7%	12	11.1%	30	10.9%

Genetic characteristics and CFTR modulator use/non-use

Among responders, 61.3% of participants identified that their or their family member's first mutation is a class I mutation and 49.4% identified that their or their family member's second mutation is a class I mutation. Among respondents, 14.2% of pwCF reported being on a CFTR modulator (i.e., Trikafta/Kaftrio, Symdeko/Symkevi, Orkambi, Kalydeco) and 14.8% of family members of pwCF reported their family members being on a CFTR modulator. **(Figure 2)**

Among pwCF, 58.0% reported being ineligible for a CFTR modulator due to CFTR mutation or lung and/or liver transplant status. Among family members of pwCF, 71.3% reported their family member being ineligible for a CFTR modulator due to CFTR mutation, lung and/or liver transplant status, or the child not being old enough yet. Ineligibility based on CFTR mutation was the most frequently reported reason pwCF were not on modulators (54.3% for pwCF and 64.8% of family members of pwCF). **(Table 3)**

FIGURE 2. What are your/your family member's mutation types?



Class 1: Protein production mutations – including nonsense mutations (i.e. G542X, W1282X, R553X), some splice mutations, and deletions
Class 2: Protein processing mutations – including F508del, N1303K, and I507del
Class 3: Gating mutations – including G551D and S549N
Class 4: Conduction mutations – including D1152H, R347P, and R117H
Class 5: Insufficient protein mutations – including some splice mutations (i.e. 3849+1-kbC-->T, 27890+5G-->A, and A455E)

TABLE 3. What is your/your family member's current modulator status?

	Adults with CF		Family members of pwCF		Total	
	n=162		n=108		n=270	
Not eligible for a CFTR modulator due to CFTR mutation	88	54.3%	70	64.8%	158	58.5%
Eligible and currently taking a CFTR modulator	19	11.7%	12	11.1%	31	11.5%
Eligible but currently not taking a CFTR modulator	19	11.7%	4	3.7%	23	8.5%
Live in a country where modulators are not available	9	5.6%	3	2.8%	12	4.4%
Not eligible for a CFTR modulator, but taking a modulator off-label	4	2.5%	4	3.7%	8	3.0%
Not eligible for a CFTR modulator due to the child not being old enough	N/A	N/A	7	6.5%	7	2.6%
Not eligible for a CFTR modulator due to lung and/or liver transplant status	6	3.7%	0	0.0%	6	2.2%
Don't know/not sure	11	6.8%	3	2.8%	14	5.2%
Other (please specify)	6	3.7%	5	4.6%	11	4.1%

Among those ineligible for CFTR modulators, 2.5% of pwCF and 3.7% of family members of pwCF reported taking or having their family member take a modulator off-label. They noted:

"Although it does not target my mutations, I have been on Trikafta since June 4 of 2021."

"Eligible for Kalydeco and Symdeko, but taking Trikafta off-label."

"Currently trying to persuade insurance to trial [my] daughter on CFTR [modulators] as her mutations are not automatically treated."

For the 19 pwCF and 4 family members of pwCF who were eligible but not taking a modulator, 68.2% cited modulator side effects as the reason, suggesting that they believed these side effects were related to modulator use. Their responses included:

"Eligible, tried it, and it destroyed my body and hospitalized me and now I am struggling health wise and so much worse than I ever was before Trikafta sadly."

"Not taking Trikafta because of his Cirrhosis of the liver – afraid the side effects or toxicity of the drug may affect his liver negatively. Right now liver is still functioning minimally."

Note: Quotes are only adjusted for spelling and grammar.

A few parents of children with CF described frustration with modulators not being as effective as they had hoped. They commented:

"We are grateful for the medication but it doesn't seem to be working for my child. Our treatment burden has actually increased since starting Trikafta. My son still has a massive 504 plan for school. We still manage 14 different medications and supplements each day. We still do at least two treatments daily and trek through airports with massive amounts of carry-on luggage. I'm happy for the people who have experienced more life changing results. But we very much feel like part of the 10%."

"We had to stop Orkambi due to transaminitis. We retried it twice with poor results. Trikafta is extremely effective, but is again causing undesirable liver and GI effects. He is on a modified dosing regimen and undergoing monthly labs. It adds an increased burden of care and anxiety for him (lab pokes) and us (liver damage, psychosocial support of a child with medical procedure anxiety). We are grateful that he meets inclusion criteria (mutation and age), however we do not feel like we can celebrate this wonderdrug, as he has been on and off so much. Additionally, there are behavioral effects (hyperactivity). We feel a sense of urgency to find medications that are more inclusive (for the 10+%) and less harsh on the body (side effects). We still worry about our child's future and prognosis."

These responses underscore the need for safer, better-tolerated therapies.

Impact of disease and treatment burden

Respondents described a spectrum of disease symptoms. The most common symptoms reported by pwCF included excessive cough (69.9%), fatigue (61.5%), pulmonary exacerbation and chronic lung infections (54.8%), shortness of breath (54.2%), and sinus disease (51.8%). Additional non-pulmonary symptoms most commonly reported by pwCF included gastrointestinal issues (47.6%) such as reflux, digestive issues such as weight challenges (41.0%), and CF-related diabetes (39.2%). **(Table 4)**

TABLE 4. Which of the following CF-related symptoms do you/does your family member experience on a regular basis?

	Adults with CF		Family members of pwCF		Total	
	n=166		n=108		n=274	
Excessive cough	116	69.9%	46	42.6%	162	59.1%
Gastrointestinal issues (i.e., digestive issues)	79	47.6%	60	55.6%	139	50.7%
Fatigue	102	61.5%	34	31.5%	136	49.6%
Pulmonary exacerbations/infections	91	54.8%	38	35.2%	129	47.1%
Sinus disease	86	51.8%	39	36.1%	125	45.6%
Shortness of breath	90	54.2%	30	27.8%	120	43.8%
Appetite/weight challenges	68	41.0%	50	46.3%	118	43.1%
Gastroesophageal issues (i.e., reflux)	61	38.6%	36	33.3%	97	35.4%
Sleep challenges	66	39.8%	31	28.7%	97	35.4%
CF-related diabetes	65	39.2%	27	25.0%	92	33.6%
Mental health issues	64	38.6%	24	22.2%	88	32.1%
Tight chest	62	37.4%	24	22.2%	86	31.4%
Chronic pain	47	28.3%	13	12.0%	60	21.9%
Hemoptysis (i.e., coughing up blood)	32	19.3%	13	12.0%	45	16.4%
Liver disease	20	12.0%	16	14.8%	36	13.1%
None	3	1.8%	6	5.6%	9	3.3%
Don't know/not sure	1	0.6%	1	0.9%	2	0.7%
Other (please specify)	9	5.4%	4	3.7%	13	4.7%

In addition to the physical symptoms, many survey respondents reported the impact of CF on their mental health. Among pwCF, 38.6% reported mental health issues. When asked about their overall mental/emotional health, 39.4% of pwCF reported their mental health status as "fair" or "poor." With regards to their own mental health, 50.9% of family members reported having "fair" or "poor" mental health status. Clearly, there is a need to address mental health issues among pwCF and family members of pwCF.

The most commonly used pulmonary treatments included airway clearance (75.5%), dornase alfa (70.4%), hypertonic saline (63.5%), inhaled antibiotics (57.2%), and azithromycin (54.7%). **(Table 5)** The most common non-pulmonary treatments were CF-specific vitamins (81.8%), enzymes (81.8%), sinus rinses (50.3%), acid blockers (44.0%), allergy medications (37.7%), and insulin (34.0%). **(Table 6)**

The significant daily treatment regimen, including treatments for both pulmonary and nonpulmonary symptoms, is a major challenge for those with CF. Most pwCF spent one to four hours a day on medical treatments (70.4% of pwCF) with 75.5% of respondents reporting doing airway clearance (i.e., Vest, positive expiratory pressure (PEP) therapy, chest physical therapy (CPT), autogenic drainage, Huff cough). **(Figure 3)**

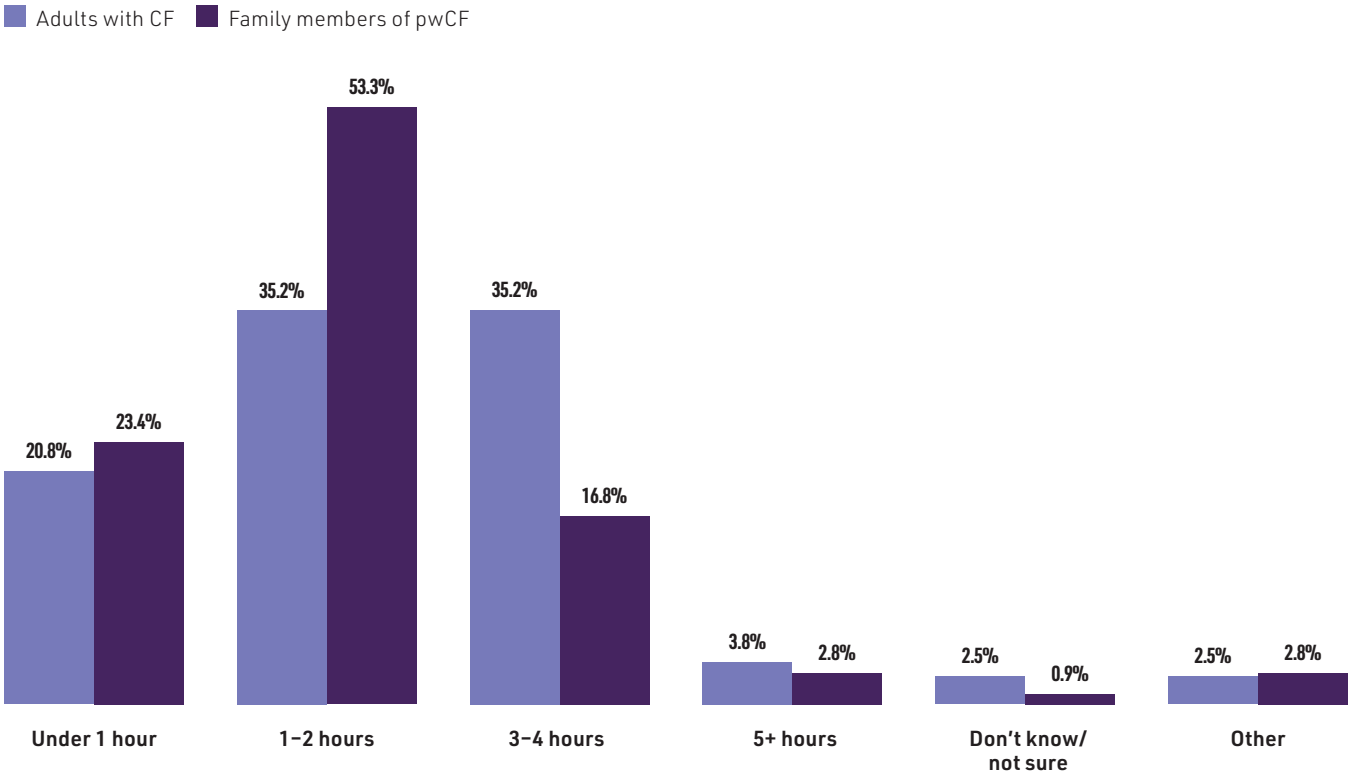
TABLE 5. What pulmonary treatments are you/your family member currently taking/utilizing?

	Adults with CF		Family members of pwCF		Total	
	n=159		n=108		n=267	
Airway clearance (i.e., Vest, PEP, CPT, Autogenic drainage, Huff cough)	120	75.5%	92	85.2%	212	79.4%
Dornase alfa (Pulmozyme)	112	70.4%	83	76.9%	195	73.0%
Hypertonic saline	101	63.5%	71	65.7%	172	64.4%
Inhaled antibiotics (i.e., TOBI, Tobi Podhaler, Cayston, Colistin)	91	57.2%	45	41.7%	136	50.9%
Oral/inhaled bronchodilators (i.e., Albuterol, Xopenex, Atrovent, Duoneb)	77	48.4%	58	53.7%	135	50.6%
Azithromycin (Zithromax)	87	54.7%	40	37.0%	127	47.6%
Inhaled corticosteroid or corticosteroid/bronchodilator combination (i.e., Pulmicort, Prednisone, Symbicort, Advair)	75	47.2%	31	28.7%	106	39.7%
Oral antibiotics (i.e., Cipro, Doxycycline, Bactrim, Augmentin)	58	36.5%	23	21.3%	81	30.3%
CFTR modulators (i.e., Trikafta/Kaftrio, Symdeko/Symkevi, Orkambi, Kalydeco)	28	17.6%	20	18.5%	48	18.0%
IV antibiotics (i.e., Tobramycin, Ceftazidime, Vancomycin)	28	17.6%	11	10.2%	39	14.6%
Oral corticosteroid (Prednisone)	28	17.6%	8	7.4%	36	13.5%
N-acetylcysteine or mucomist	24	15.1%	9	8.3%	33	12.4%
Oxygen therapy	27	17.0%	3	2.8%	30	11.2%
Antifungals for lungs (i.e. Voriconazole, Itraconazole, Posaconazole)	6	3.8%	12	11.1%	18	6.7%
Biologics (Dupixent)	3	1.9%	3	2.8%	6	2.3%
None	3	1.9%	1	0.9%	4	1.5%
Don't know/not sure	0	0.0%	4	3.7%	4	1.5%
Other (please specify)	5	3.1%	5	4.6%	10	3.8%

TABLE 6. What non-pulmonary treatments are you/your family member currently taking/utilizing?

	Adults with CF		Family members of pwCF		Total	
	n=159		n=107		n=271	
Enzymes (i.e., Creon, Zenpep, Pancreaze, Ultresa, Viokace, Pertzye)	130	81.8%	97	90.7%	227	83.8%
CF-specific fitamins (i.e., Vitamins A, D, E, and K)	130	81.8%	86	80.4%	216	79.7%
Sinus rinses	80	50.3%	42	39.3%	122	45.0%
Acid blockers (i.e., Prilosec, Prevacid, Zantac)	70	44.0%	41	38.3%	111	41.0%
Allergy medications	60	37.7%	40	37.4%	100	36.9%
Oral supplemental feeds (i.e., Scandishakes, Pediasure)	40	25.2%	44	41.1%	84	31.0%
Insulin (i.e., Humalog, Fiasp, Lantus, Levemir, Tresiba)	54	34.0%	24	22.4%	78	28.8%
Polyethylene glycol (i.e., Miralax, GoLYTELY)	37	23.3%	25	23.4%	62	22.9%
Mental health medications	42	26.4%	12	11.2%	54	19.9%
Ursodeoxycholic acid	15	9.4%	14	13.1%	29	10.7%
Immunosuppressants (i.e., Prograf, Cyclosporine, Cellcept, Prednisone)	23	14.5%	5	4.7%	28	10.3%
Enteral tube feeds via NG tube, G-Tube, J-Tube, TPN	9	5.7%	17	15.9%	26	9.6%
Other transplant-related medications and vitamins	17	10.7%	5	4.7%	22	8.1%
Transplant-related anti-infectives (i.e., Bactrim, Valcyte, Valtrex)	14	8.8%	4	3.7%	18	6.6%
Oral diabetes medication (i.e., Repaglinide/Prandin)	6	3.8%	2	1.9%	8	3.0%
None	3	1.9%	2	1.9%	5	1.8%
Don't know/not sure	0	0.0%	2	1.9%	2	0.7%
Other (please specify)	12	7.5%	2	1.9%	14	5.2%

FIGURE 3. How much time do you/your family member spend doing medical treatments each day?



In addition to at-home management, many pwCF require hospitalizations for treatment of lung exacerbations, GI issues, and other complications of CF. A majority (52.4%) reported being hospitalized in the past year. Of note, 14.9% of respondents reported being hospitalized more than 5 times in the past year. Among respondents, 11.7% had a lung transplant and 4.3% were listed for transplant.

Treatment burden and the time required for daily therapies was reported as "moderately" or "significantly" burdensome by 83.0% of pwCF, underscoring the need for less time-consuming treatments. As one pwCF said:

> *"I've always thought it would significantly help reduce the burden of CF if every therapy/antibiotic was in pill form. It would be much easier to travel and live a more seemingly normal life if I only had to pop pills every day. I wouldn't even mind if it took 50 pills a day if I didn't have to lug my vest around or go in the hospital anymore."*

The other aspects of CF most commonly reported as "moderately" or "significantly" burdensome were avoiding germs (80.7%), feeling isolated or like a burden to others (78.1%), and fear of running out of treatment options (including antimicrobial resistance) (76.9%).

pwCF reported that CF had a significant impact on their daily lives. The most frequently cited areas of "significant" or "moderate" impact were plans for the future (in general) (83.1%), daily life in general (83.0%), and staying healthy for your dependents (81.2%). **(Table 7)**

TABLE 7. How much does CF impact the following aspects of daily life?

Respondents indicating "significant" or "moderate" impact

	Adults with CF		Family members of pwCF		Total	
Your daily life in general	127	83.0%	75	70.8%	202	78.0%
Plans for the future (in general)	128	83.1%	65	66.3%	193	76.6%
Finances	112	74.7%	63	73.3%	175	74.2%
Staying healthy for your dependents	95	81.2%	28	53.9%	123	72.8%
Ability to spend time with friends/participating in social activities	113	72.4%	75	72.1%	188	72.3%
Mental health (i.e., anxiety or depression)	114	75.0%	65	66.3%	179	71.6%
Travel	122	79.2%	60	59.4%	182	71.4%
Family planning (i.e., starting a family)	83	73.5%	34	60.7%	117	69.2%
Work or employment issues (i.e., finding and keeping a job)	94	70.7%	36	62.1%	130	68.1%
Participation in sports, hobbies, or extracurricular activities	105	71.4%	59	57.8%	164	65.9%
School issues (i.e., staying on top of school work, handling medication and health issues at school)	47	54.0%	49	56.3%	96	55.2%
Relationships issues (i.e., dating)	88	60.3%	26	41.9%	114	54.8%
Pursuit of higher education/professional or vocational training	69	54.3%	42	53.2%	111	53.9%
Ability to live independently	74	49.3%	40	51.3%	114	50.0%
Ability to obtain or keep health insurance	56	44.8%	30	37.0%	86	41.7%
Other (please specify)	11	64.7%	6	66.7%	17	65.4%

Impact of lack of opportunity to benefit from modulators

While most pwCF in the final 10% felt happy that others were benefiting from current CFTR modulators, many pwCF and family members of pwCF reported fear and a sense of despair. They said:

*"I really really struggled with this. **I feel completely left out, sad, and angry.** I have become very bitter and negative towards my existing treatments and the CF team because there has been nothing new available to me for years."*

*"**Disappointing, sad, lonely.**"*

*"Feel **marginalized**."*

*"**Happy for them. Heartbroken for us.**"*

*"I'm really happy for them. I am so thrilled to see their improvement over a matter of weeks. However I can't help but feel a little sad for me and my family. Staying well for my kid is everything to me. **I would love a chance to be here for longer.**"*

*"Makes me hopeful of the direction that the CF research community is heading in, but also **worried that efforts to find a cure for all might reduce or slowly tail off now that 90% of CF patients are greatly benefiting from new therapies.**"*

*"Good for them. But **hard to see that time is slipping away for the 10%,** especially as our CFer is aging and seeing increased impact from CF."*

*"**Bittersweet**, but very worried that they will forget about the last 10%."*

*"I'm happy for them but deep inside I'm angry. **My son deserves the same chance to live a healthier life as the other 90%.**"*

*"Having CF in the final 10% has affected my daughter's mental health, she struggles to fit in with her friends without CF and now she struggles with her online friends with CF due to them being on the modulators and feeling so much better with no admissions, whereas she's had five hospital stays due to IVs, partial collapse lung, bowel blockages, port fitted, sinus surgery and a blood clot all in one year. **She's happy for all of her CF friends but it is taking a massive toll on her mental health**."*

The fear of being forgotten or left behind was also a common theme that emerged among pwCF and their family members. They said:

*"My adult child with CF has stated that **the worst CF issue she deals with is depression and being part of the 10% has made it worse**. She is very happy for the 90%, but it is painful to be left behind. So I believe that treatment plans to address the mental health aspect of being part of the 10% are very important. Even small things like doctors and nurses not continually asking if they are on modulators would help... every time that question is asked, especially by a medical professional, it is a reminder that they are not eligible."*

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*"Encouraged for the community but **sad and alone** for our loved one."*

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*"I really really struggled with this. I feel completely **left out, sad, and angry**. I have become very bitter and negative towards my existing treatments and the CF team because there has been nothing new available to me for years."*

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*"It is very very difficult. **I feel fear that we will be forgotten**, since most of the people with CF will get medications and medical companies will find no interest in looking for medications for rare mutations."*

Equity and access

While approximately 90% of pwCF in HIC have mutations that make them eligible to CFTR modulators, access to the modulators remains a challenge and contributes to health disparities among pwCF globally. In many countries, modulators are still not available.[1] In the survey, 5.6% of pwCF and 2.8% of families of pwCF reported living in a country where modulators are not available. It is important to note that these percentages reflect responses on a survey for individuals that are not benefitting from CFTR modulators and do not reflect the total percentage of individuals with CF that live in countries where modulators are not available, which is markedly higher.

In addition, many countries lack diagnostic and genetic analysis capabilities, which means that the number of pwCF with mutations that could benefit from CFTR modulators may be higher than previously reported.[1] Furthermore, there may be understudied rare mutations that could benefit from CFTR modulators but have not been tested yet.

The need for additional testing to explore expanded use of CFTR modulators was commonly noted in survey responses. One parent of a pwCF said:

"My son's specific mutation that could respond to a modulator is H609R. His other one is a Class I so it won't. H609R has only been found in Ecuadorean populations. In fact, a recent research study revealed that in Ecuador it is just as common as Delta F508. I would love if there was a modulator available specific to the function of H609R or in general, if researchers started developing modulators specific to certain mutations that are rarer."

CF community perspectives on future treatments of CF

If a new therapy was being developed but it was not a complete cure, the health issues that were deemed most important to treat by survey respondents included lung function (FEV1) (75.8%), lung infections/exacerbations (59.1%), and antibiotic resistance (46.2%). **(Table 8)**

TABLE 8. If a new therapy was being developed but it was not a complete cure, which aspects of CF would be most important for the new treatment to address? (Please select up to 4 responses)

	All respondents	
	n=264	
Lung function (FEV1)	200	75.8%
Lung infections/exacerbations	156	59.1%
Antibiotic resistance	122	46.2%
GI/digestive issues	87	33.0%
CF-related diabetes	84	31.8%
Fatigue and reduced energy	70	26.5%
Sinus disease	50	18.9%
Improved weight/BMI	41	15.5%
CF-related liver disease	33	12.5%
Depression/anxiety	28	10.6%
Post transplant complications (i.e., cancer risk, immunosuppressant side effects)	20	7.6%
Hemoptysis (lung bleeds)	18	6.8%
Pain	17	6.4%
CF-related arthritis	15	5.7%
Other (please specify)	4	1.5%

When asked what aspects of CF would be most important for new treatments to address, survey respondents said:

LUNG FUNCTION

"Improving my lung function is everything to me. Absolutely everything. Because improved lung function means clearer lungs, which means more air, which means more energy, which means being able to stay well for longer for those I love in my life."

INFECTIONS/EXACERBATIONS

"Better treatment for exacerbations. Less heavy IVs which cause significant reactions and side effects. More opportunity to eradicate infections."

ANTIBIOTIC RESISTANCE

"My undiagnosed CF has led to being antibiotic resistant, which is a high challenge for me now. I would love ANY treatment to help with my Mycobacterium abscessus lung disease."

"More antibiotics because I am almost out of options. New more effective airway clearance."

pwCF and their family members had a range of opinions on what they would look for in a future CF therapy, short of a cure. They said:

"I don't need perfect. I would just like it to be better. :)"

"I just wish for a life without constant coughing. Coughing bothers me in every situation."

"Medication that improves lung function and energy."

"Anything that could make breathing easier. Anything that could reduce the cough. Anything that could effectively remove inflammation. Most mornings when I wake up, I struggle to breathe and it takes an hour of sitting up right, taking nebulisers and coughing before I can properly function. Sometimes I wake up and my whole body feels inflamed. My chest feels like it has had a friction burn, my face hurts, my sinuses burn, my skin is tight and my joints hurt."

"Increase in lung function and increase in energy would be amazing and just something to make me stable."

"Just something that lets me breathe easier. Even if my lung function increased by a few % that would give me comfort and I would be comfortable functioning at that level for the rest of my life. I would like it to eliminate the potential for decline."

CF community perspectives on clinical trials

The CF community is highly motivated to take part in clinical trials. **(Figure 4)** Of those that responded, 50.3% of pwCF reported they had previously participated in a clinical trial and 83.0% reported that they would be willing to participate in a future clinical trial. Even those that had not participated in previous trials expressed a willingness to enroll in future trials (37.3%). The most common reasons stated for being motivated to enroll in trials was the possibility of improving their health (89.7%), desire to help find a cure (87.3%), desire to help the CF community even if the trial does not directly help the participant (65.9%), and free access to new study drugs (58.7%). **(Table 9)**

FIGURE 4. Have you/your family member participated in a clinical trial?

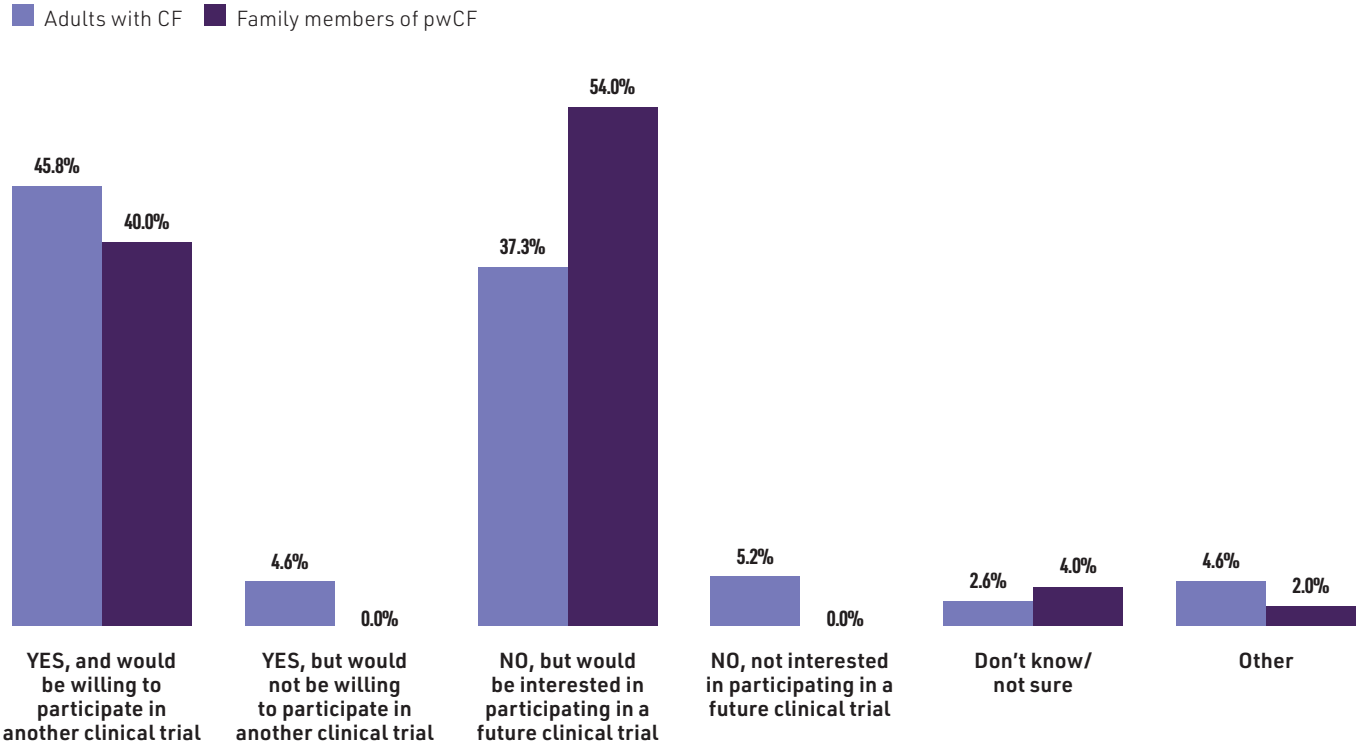

TABLE 9. What are the main reasons you/your family member would be motivated to enroll in a CF clinical trial? (Please select all that apply)

	Adults with CF		Family members of pwCF		Total	
	n=126		n=94		n=220	
Possibility of improving my health	113	89.7%	83	88.3%	196	89.0%
Desire to help find a cure	110	87.3%	69	73.4%	179	80.4%
Desire to help the CF community, even if it doesn't help me	83	65.9%	46	48.9%	129	57.4%
Free access to new study drugs	74	58.7%	45	47.9%	119	53.3%
Better care and attention from my care team	47	37.3%	28	29.8%	75	33.5%
Positive results of a previous trial	42	33.3%	25	26.6%	67	30.0%
Compensation for participation	36	28.6%	12	12.8%	48	20.7%
Other (please specify)	0	0.0%	2	2.1%	2	1.1%

For respondents that reported not being interested in participating in future trials, the main reasons were not wanting to go off current medications and/or change medication schedule (46.7%), concern over possible negative side effects/that the participant's health will get worse (40.0%), and concerns about study procedures (26.7%). Of note, among those that responded, 13.3% of pwCF cited not being asked by anyone at their care center for why they were not participating. **(Table 10)**

TABLE 10. What are the main reasons you have not or would not want to participate in a CF clinical trial? (Please select all that apply)

	Adults with CF	
	n=15	
Not wanting to go off current medications and/or change medication schedule	7	46.7%
Concern over possible negative side effects; that my health will get worse	6	40.0%
Concern about study procedures (i.e., extra blood draws, x-rays)	4	26.7%
Concern that the study drug isn't going to work	2	13.3%
Not being asked by anyone at my care center/did not know about them	2	13.3%
Not qualifying for the trial (Because of health status, age, transplant status, etc...)	2	13.3%
Not wanting to potentially receive a placebo instead of an active drug	2	13.3%
Concern that I would not be able to get the study drug after the trial ends	1	6.7%
Not being able to participate in other trials that come around	1	6.7%
Not having enough information about what the trial entails	1	6.7%
Other (please specify)	1	6.7%

Conclusion

In 2012, the first CFTR modulator that treated the basic defect of CF was approved in the US. By 2019, there were four approved CFTR modulators in the US, including two that substantially improve CFTR function, pulmonary health, and quality of life, and that are dramatically changing the clinical course and life expectancy of pwCF. Approximately 90% of the pwCF are eligible for these modulators based on their age and mutations, leaving a group of approximately 10% that remain ineligible.

In addition, there are many pwCF that are unable to tolerate the therapies or who lack access based on where they live. The "Final 10% Survey" captured information on demographics, clinical characteristics, impact of disease, and clinical research preferences and perspectives on future therapies among pwCF not benefiting from approved modulators and their family members across six continents.

The results of the 2022 "Final 10% Survey" show that pwCF not benefiting from modulators continue to have substantial symptoms and treatment burden. Consequently, their quality of life and their mental health are adversely impacted. Furthermore, the knowledge that there are life-changing medications available to some pwCF, but not all creates further distress. Nonetheless, many pwCF not eligible for modulators have participated and/or would consider participating in a clinical trial for their own potential benefit and also to help others with CF, highlighting the altruism of the CF community. In summary, data from the 2022 "Final 10% Survey" survey was generally consistent with data from the 2021 "Final 10% Survey" but with a lower response rate in 2022.[2] As a result, we plan to conduct the survey again in a few years or sooner in the event of a significant change that might impact survey results.

As laboratory scientists and clinical investigators continue working towards a cure for CF, pwCF and their family members are hoping for a future free of the burdens of CF. When asked what they would look forward to most with a cure, they responded:

"A third pregnancy, hopefully."

"Breathing."

"A long and fulfilling life with my wife."

"A future with my soon to be hubby and children (God willing), and no fear of transplantation."

"Active life and pursuing my dreams without uncertainty of health decline."

"Laughing without coughing. With pure joy."

"All patients can get this medicine without distinguishing between race, religion or color."

Our deepest desire is that the work of EE can help make these hopes and dreams come true for 100% of the CF community as soon as possible.

To read the 2021 "Final 10% Survey" results, please visit pubmed.ncbi.nlm.nih.gov/35170259.

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