

# UCSF

## UC San Francisco Previously Published Works

### Title

Left behind: The potential impact of CFTR modulators on racial and ethnic disparities in cystic fibrosis

### Permalink

<https://escholarship.org/uc/item/3j93c88t>

### Journal

Paediatric Respiratory Reviews, 42

### ISSN

1526-0542

### Authors

McGarry, Meghan E  
Gibb, Elizabeth R  
Oates, Gabriela R  
[et al.](#)

### Publication Date

2022-06-01

### DOI

10.1016/j.prrv.2021.12.001

Peer reviewed



Published in final edited form as:

*Paediatr Respir Rev.* 2022 June ; 42: 35–42. doi:10.1016/j.prrv.2021.12.001.

## Left Behind: The Potential Impact of CFTR Modulators on Racial and Ethnic Disparities in Cystic Fibrosis

Meghan E. McGarry, MD, MAS<sup>1</sup>, Elizabeth R. Gibb, MD<sup>1</sup>, Gabriela R. Oates, PhD<sup>2</sup>, Michael S. Schechter, MD MPH<sup>3</sup>

<sup>1</sup>Division of Pulmonary Medicine, Department of Pediatrics, University of California San Francisco, San Francisco, CA

<sup>2</sup>Division of Pulmonary and Sleep Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL

<sup>3</sup>Division of Pulmonary and Sleep Medicine, Department of Pediatrics, Virginia Commonwealth University and Children's Hospital of Richmond at VCU, Richmond, VA

### Abstract

The advent of CFTR modulators, a genomic specific medication, revolutionized the treatment of CF for many patients. However, given that these therapeutics were only developed for specific *CFTR* mutations, not all people with CF have access to such disease-modifying drugs. Racial and ethnic minority groups are less likely to have *CFTR* mutations that are approved for CFTR modulators. This exclusion has the potential to widen existing health disparities.

### Keywords

cystic fibrosis; CFTR modulators; race; ethnicity

### Introduction

Racial and ethnic minorities make up a growing proportion of patients with cystic fibrosis (CF), currently accounting for 18% of all people in the CF Foundation patient registry.<sup>1</sup> The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, genomic-specific medications that target the malfunctioning protein made by the *CFTR* gene, has revolutionized the treatment of CF for many patients. However, CFTR therapeutics are mutation-specific, and racial and ethnic minority groups are less likely to have *CFTR*

#### Conflict of Interest/Funding:

McGarry - 2 grants:  
CFF MCGARR20A0-KB  
NHLBI K23HL133437  
Oates - 1 grant  
NIH P30DK072482

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

mutations targeted by CFTR modulators. This constraint of access to disease-modifying CFTR therapies can widen existing health inequities in CF. This review examines the cautionary tale of the disparities that can result from precision medicine when some population groups are left out of the advancements in therapeutics.

### **Socioeconomic, racial, and ethnic disparities in CF outcomes**

The introduction of CFTR modulator therapy is superimposed upon a backdrop of significant heterogeneity of CF disease outcomes that is caused not only by genetic variability but also by disparities in social determinants of health, including those associated with socioeconomic status, race, and ethnicity<sup>2</sup>. Studies over the last 25 years have clearly demonstrated large decrements in lung function, growth, and survival in CF patients with low socioeconomic position as indicated by insurance status (in the U.S.)<sup>3,4</sup>, educational status, family income<sup>5</sup>, and parental occupation (in the U.K.)<sup>6</sup> in all countries where it has been examined, primarily the U.S. and the U.K.

In the U.S., several studies have shown that racial and ethnic minorities have increased morbidity and mortality from CF compared to non-Hispanic White patients, even when controlling for socioeconomic status. These patients are more likely to be missed on genetic panels and state newborn screening and be diagnosed later.<sup>7–10</sup> Hispanic people with CF in the U.S. have an increased risk of mortality compared to non-Hispanic White people and die at an earlier age.<sup>11–13</sup> Black people with CF also have an increased risk of mortality compared to non-Hispanic White people.<sup>13</sup> One study of risk factors for mortality before age 18 years found increased risk for both non-White versus White subjects and for a combined “minority” group compared to non-Hispanic White subjects.<sup>14</sup> Both Hispanic and Black people with CF have lower pulmonary function compared to non-Hispanic White people with CF.<sup>10,15–17</sup> Hispanic people with CF are at increased risk of acquiring pulmonary infections compared to non-Hispanic White people with CF and acquire infections at an earlier age.<sup>18,19</sup> Notably, disparities in CF outcomes by Hispanic ethnicity occur despite higher BMI and a larger proportion of residual function pancreatic sufficient *CFTR* mutations in the Hispanic population.<sup>20</sup> Differences in morbidity or mortality have not yet been investigated specifically in Asian, Pacific Islander, Native American, or Native Alaskan people with CF in the U.S., and we are aware of no studies of ethnic and racial disparities in CF outcomes outside of the U.S..

There are some differences in the distribution of *CFTR* mutations by race and ethnicity (described in more detail below), and as a result, newborns who are not non-Hispanic White are more likely to be missed on state newborn screening for CF, delaying diagnosis and potentially impairing outcomes, especially growth.<sup>7,9,10</sup> It is essential to recognize that racial and ethnic disparities in health, CF-related and otherwise, are largely attributable to unequal social conditions and deeply rooted structural inequalities.<sup>21–23</sup> For example, both Black and Hispanic people with CF reside in neighborhoods with lower median household income and have higher Medicaid coverage than non-Hispanic white counterparts.<sup>24</sup> Understanding the racial/ethnic disparities in CF also requires careful consideration of the effects of psychosocial factors, health literacy and acculturation, and stress and racism. For example,

African American and Hispanic patients report worse emotional and social functioning after controlling for disease severity and socioeconomic position.<sup>25</sup>

On a global level, there are great disparities in CF disease outcomes, including growth and nutrition, lung function, quality of life, and life expectancy, attributable to regional wealth. For example, the median age of survival of patients with CF in different countries is closely tied to those countries' gross domestic product or stage of industrialization; while life expectancy in Canada, the USA, and European Union (EU) countries is in the mid-40s or above, it is half of that in some Latin American countries, and even less in some countries of the former Soviet Union.<sup>26</sup>

### CFTR modulators

The over 2,000 *CFTR* mutations discovered<sup>27</sup> have been classified based on the functional impact of the mutation: Class I mutations have decreased biosynthesis of protein, Class II mutations have decreased mature protein due to impaired trafficking, Class III mutations have defective *CFTR* gating regulation, Class IV mutations have defective chloride conductance, and Class V mutations have decreased *CFTR* transcription.<sup>28</sup> *CFTR* mutation classes I-III are considered severe, with minimal function, and result in classic CF disease. *CFTR* mutation classes IV-V are considered less severe, with residual function, and can result in milder CF disease.

Prior to 2012, all CF therapeutics were genomic-neutral and prescribed based on disease characteristics, such as pulmonary function or a specific infection. The treatment of CF entered a new era on January 31, 2012, with the U.S. FDA approval of ivacaftor, the first *CFTR* modulator drug. Ivacaftor potentiates the *CFTR* channel, increasing chloride conductance and thereby correcting fluid balance across the airway apical cell membrane. This was the first therapeutic agent that targeted the cause of CF rather than its symptoms.

Ivacaftor was first approved for only one *CFTR* mutation, G551D, a class III (gating) mutation that represents approximately 4% of patients with CF in the United States and 3–6% of those from Northern Europe, depending upon country of origin. The clinical trial of ivacaftor showed dramatic improvement in patients with a copy of G551D: increased pulmonary function, weight gain, reduced sweat chloride concentration, improved respiratory symptoms, and fewer pulmonary exacerbations.<sup>29</sup> From case reports and other clinical trials, however, it quickly became apparent that ivacaftor would benefit patients with additional *CFTR* mutations that are functionally similar to the G551D.<sup>30–34</sup> Consequently, FDA approval for ivacaftor was expanded to cover other class III *CFTR* mutations as well as R117H, a class IV *CFTR* mutation. Nevertheless, only a relatively small percentage of people with CF had the mutations that qualified them to receive this disease-altering drug.

Over the years, new *CFTR* therapeutics – the *CFTR* correctors lumacaftor, tezacaftor, and elexacaftor – were developed to target class II *CFTR* mutation classes found in the majority of people with CF. *CFTR* correctors chaperone the mutated *CFTR* protein in folding and trafficking to increase the number of *CFTR* in the basement membrane. *CFTR* correctors are effective only when their function is augmented by potentiators such as ivacaftor. Lumacaftor/ivacaftor, approved for clinical use in the U.S. in July 2015, was the first *CFTR*

corrector for people with two copies of F508del, the most common CFTR mutation.<sup>35</sup> In February 2018, the U.S. FDA approved tezacaftor/ivacaftor for people with two copies of F508del or one copy of F508del and one copy of *CFTR* mutations associated with residual function. The triple therapy elexacaftor/tezacaftor/ivacaftor was first approved by the FDA in October 2019 for people 12 years and older with one copy of F508del, later expanded to 177 other CFTR mutations and, in June 2021, approved for children 6–11 years of age.

Not all CFTR therapies have had the dramatic disease-altering results as ivacaftor had with G551D. Lung function improved only slightly with lumacaftor/ivacaftor<sup>36,37</sup> and tezacaftor/ivacaftor,<sup>38–40</sup> although the two drugs also seemed to stabilize disease course, and reduced exacerbation frequency.<sup>36,38,41</sup> In contrast, elexacaftor/tezacaftor/ivacaftor produced more impressive results, with improved lung function and sweat chloride concentration<sup>42</sup> similar to ivacaftor in G551D. Thus, lumacaftor/ivacaftor and tezacaftor/ivacaftor are considered low-efficacy CFTR modulators, whereas ivacaftor and elexacaftor/tezacaftor/ivacaftor are highly effective CFTR modulators that are expected to markedly improve the lifespan of people with CF. As approval of CFTR modulators is based on CFTR genetic mutations, access to these drugs is not equal across all people with CF. Approximately 90% of CF patients in the United States have a mutation that is correctable by a CFTR modulator. For the rest, high-efficacy CFTR therapy leading to improved disease course is not an option.

### CFTR mutations by country of origin, race and ethnicity

CF occurs across the world and in people of all races and ethnicities.<sup>43,44</sup> It is thought that F508del and a few other, common mutations originated between 11,000 and 34,000 years ago in a population genetically different from any present-day European group, and subsequently spread to different areas of Europe and beyond. The incidence of the disease as well as the frequency of the most common mutations probably reflect ancient migratory and demographic expansion processes, and possibly a selective advantage of heterozygous carriers. Some mutations seem to have been subject to founder and genetic drift events, thus explaining regional heterogeneity.<sup>45</sup> Thus, the variation in *CFTR* mutation frequency and type is not uniform within racial or ethnic groups; rather, it is dependent on an individual person's ancestry admixture.<sup>7,9,46</sup> F508del has a frequency of about 70% in across central, northern, western, and northeastern Europe, but the regional frequency varies from 100% in the Faroe Islands of Denmark to 20% in Turkey. The *CFTR* mutation profile in sub-Saharan Africans has revealed a common African mutation, 3120+1G→A, which is found on about 46% of the *CFTR* alleles in people diagnosed with CF from that region. That mutation is also the second most common one found in African-Americans with CF.<sup>47</sup> The prevalence of F508del in Latin America varies substantially by country, reflecting the ancestral makeup of the population: nearly 60% in Argentina and Uruguay, around 40% in Brazil, Chile, Colombia, Mexico, and Venezuela, and lowest (20–30%) in Puerto Rico, Cuba, Ecuador, and Costa Rica. There is only a 10% prevalence in people with CF in the Dominican Republic.<sup>48</sup> People with CF in Costa Rica have a higher prevalence of the Class 1 mutation G542X than of F508del.<sup>45</sup> Similarly, the F508del mutation is found to a varying degree in different Middle Eastern populations; in particular, Ashkenazi Jews in Israel have a high prevalence of Class 1 mutations such as W1282X, and other population subsets from that region exhibit a variety of indigenous mutations. Finally, in Asia, where the overall prevalence of CF

appears to be low, the frequency of F508del is as high as 60% in Pakistani CF patients, but closer to 20% in those from India and 10% of those in Japan.<sup>47</sup>

In the United States, almost 75% of non-Hispanic White people with CF have Class I-III mutations, compared to approximately 50% of Black, Hispanic, and people of other races with CF.<sup>49</sup> Approximately 25% of Black, Hispanic, and people of other races with CF have unclassified *CFTR* mutations, compared to only 11% of non-Hispanic White people with CF.<sup>49</sup> Only 3% of non-Hispanic White people with CF do not have two identified *CFTR* mutations; in contrast, 8–10% of Black, Hispanic, and people of other races with CF have at least one *CFTR* mutation that is not identified.<sup>49</sup>

It is important to note that these differences in allele frequency mean that non-Hispanic White newborns with CF are more likely to be missed on state newborn screening for CF.<sup>50</sup> It is therefore important to consider the impact of newborn screening methodologies to prevent embedding health disparities into public health programs such as state newborn screening for CF. These children who are missed on the newborn screen are diagnosed later and at risk of experiencing significant malnutrition and pulmonary damage at the time of diagnosis. These same children are at higher risk of not qualifying for *CFTR* modulator therapy, augmenting their risk for poor outcomes.

### Access to *CFTR* modulators in racial and ethnic minority groups

Due to the racial and ethnic differences in *CFTR* mutation frequency, there are large disparities in access to the tremendous therapeutic advances provided by treatment with *CFTR* modulators. While over 90% of non-Hispanic White people with CF in the U.S. have *CFTR* mutations that qualify for a *CFTR* modulator, only 70% of American Black, 75% of Hispanic, and 80% of other racial minorities with CF have qualifying mutations.<sup>49</sup> This inability to take advantage of *CFTR* modulators is likely to exacerbate pre-existing racial and ethnic disparities in CF outcomes such as pulmonary function and somatic growth.

The disparities in *CFTR* modulator use are not attributable solely to racial/ethnic differences in *CFTR* mutations. Even among people with a copy of G551D, uptake of ivacaftor has been found to be significantly lower in American adults from other races or ethnicity compared to non-Hispanic White adults.<sup>51</sup> A similar evaluation of prescription of lumacaftor-ivacaftor did not differentiate by race or ethnicity but did find higher rates of *CFTR* modulator prescription to patients with private insurance and previous clinical trial participation, and racial and ethnic minorities in the US are less likely to be in either of those groups.<sup>52</sup> The cause or causes of this difference is unclear. Providers may be more reluctant to prescribe *CFTR* modulators to racial/ethnic minorities because few clinical trials of *CFTR* modulators provided data on race/ethnicity, and the study population was predominantly non-Hispanic White.<sup>53</sup> Differential prescription of *CFTR* modulators by race and ethnicity may also be indicative of implicit bias as reported for prescription of other medications in the general population.<sup>54–57</sup>

On the other hand, the disparity in *CFTR* modulator use may also be attributable to patient attitude towards this new medication class. For example, in U.S. adults with Type 1 diabetes, patients from racial and ethnic minority backgrounds were more likely to worry about drug

side effects and be reluctant to add new medications.<sup>58</sup> But even if not actively opposed to starting a new medication, minority patients may have a lesser tendency to advocate for or seek out prescriptions for the new medications, which may be easier for those with a higher sense of empowerment. Thus, for example, in a previous study of the use of chronic CF medications, the only medication that was less likely to be prescribed to patients on public assistance compared to those with private insurance was azithromycin, which at the time was a relatively new addition to the therapeutic armamentarium that was slowly being adopted and whose role was just being established at the time.<sup>59</sup> Similarly, a recent evaluation of the impact of a quality improvement program focused on improving the consistency of treatment of pulmonary exacerbations showed that the intervention had a differential impact on patients of lower socioeconomic class, again possibly due to this group's lower sense of empowerment in advocating for treatment for their children.<sup>60</sup> Thus, lower confidence in their interactions with healthcare providers, which may be due to prior experiences of discrimination or due to lower levels of health literacy, or other competing needs (such as housing or food insecurity) which limit patients' and families' ability to focus on specific healthcare needs may reduce the likelihood that they will be prescribed effective medications by busy practitioners who may be inconsistent in their treatment approach.

### **Access to CFTR modulators across the world**

Despite the dramatic benefit of the new highly effective CFTR modulators, access to them is restricted to higher-resource countries due to their record-breaking cost, which could be more than \$15 million over the life of an individual and \$2 billion yearly for all people with CF in the United States alone.<sup>61–64</sup> As a result, only 11 countries and the European Union have approved at least one CFTR modulator, and only 9 countries and the European Union have approved all four modulators (Table 1);<sup>65,66</sup> not all countries have approved modulator use for all eligible CFTR mutations.

Unequal access to CFTR modulators across the world will increase the already stark disparities in CF morbidity and mortality between countries.<sup>44</sup> Notably, the countries with approval of CFTR modulators have a predominantly White Western European population. People with CF in Eastern Europe, Asia, Africa, or most of South America have no access to CFTR modulators.

### **Inclusion/exclusion of minorities in CF clinical trials**

Very few pharmacology clinical trials in CF included patients who are racial/ethnic minorities.<sup>53</sup> From 1999 to 2015, 80% of all CF pharmacology clinical trials did not even describe the race and/or ethnicity of the subjects. Some FDA-approved CF medications did not report race or ethnicity for any of the subjects. Of the 20% of clinical trials that described race and ethnicity, minority patients were included at lower proportions than reported in the U.S. CF Foundation Patient Registry. When reported, nearly all of the subjects in CF pharmacology clinical trials were non-Hispanic White, and a quarter of the trials included only non-Hispanic White subjects.

The same was true for clinical trials of CFTR modulators (Figure 1). Of 9 of the 23 manuscripts reporting results from ivacaftor clinical trials that even reported race and

ethnicity, two manuscripts had 100% non-Hispanic White subjects,<sup>67,68</sup> five had 97–98% non-Hispanic White subjects,<sup>29,69–72</sup> one had 71% non-Hispanic White subjects,<sup>31</sup> and one had 57% non-Hispanic White subjects.<sup>73</sup> Three of the four lumacaftor/ivacaftor studies that reported on race included 97–100% White subjects,<sup>74–76</sup> The one tezacaftor/ivacaftor clinical trial that reported the subjects' race, included 99% White subjects;<sup>77</sup> none of the studies reported on ethnicity,<sup>38–40,78–81</sup>. The one of seven elexacaftor/tezacaftor/ivacaftor clinical trial manuscripts that reported subject race and ethnicity<sup>42,82–86</sup> had 90% White subjects.<sup>87</sup> Two of the manuscripts described the subjects' race and ethnicity after inquiries in Letters to the Editor.<sup>88,89</sup>

Although part of the reason for the low participation of minority patients in CFTR modulator trials is the relatively lower prevalence of qualifying *CFTR* mutations for these drugs, This is not the full explanation, as racial/ethnic minority patients are under-included in clinical trials even after accounting for the relative prevalence of genetic mutations.<sup>53</sup> Despite the common belief that low participation of minorities in CF clinical trials is based upon choice, it has been shown in the general population that minorities who are actually asked to participate in clinical trials have the same or higher rate of consenting to participate as non-Hispanic White patients.<sup>90</sup> Rather, the explanation may lie in differential access to CF clinical trials, racial/ethnic diversity of CF centers selected for clinical trials, or racial and ethnic bias in recruitment by study coordinators. Lack of inclusion of Hispanic patients may also be related to lack of translated material or interpreter availability. Significant efforts should be devoted not only to recruit subjects that reflect the actual diversity of the CF population, but also to recruit enough subjects from racial/ethnic minority backgrounds so differences in adverse events, drug metabolism, or therapeutic benefit could be detected.

Exclusion of racial/ethnic minority groups from clinical trials is not limited to CF. It is a widespread issue that necessitated a U.S. Federal Law requiring that minority groups are included in NIH-funded research.<sup>91</sup> Unfortunately, these inclusion criteria have not been adopted by the pharmaceutical industry or the CF Foundation, which sponsors the majority of CF clinical trials in North America. Additionally, despite recent guidelines,<sup>92</sup> many medical journals have not yet developed standards that require the reporting of subjects' race and ethnicity for all clinical trials.

The lack of inclusion of racial/ethnic minorities in clinical trials of CFTR modulators has many implications. Due to under-representation, it is not known if there are differences in adverse events, drug metabolism, or therapeutic response in people with CF from racial/ethnic minority background. Racial and ethnic minorities with CF may have concerns about the drugs' safety and side effects, declining to take them when offered. People with CF from racial and ethnic minority backgrounds may also lack knowledge about CFTR modulators, leading to decreased use in these groups.

### **Expansion of CFTR modulators to rare and novel mutations**

To achieve equitable access to CFTR modulators for racial and ethnic minorities with CF, these therapeutics' efficacy needs to be tested for rare or de novo CFTR mutations. Many efficacy studies of CFTR modulators were designed as traditional clinical trials, with one group receiving the treatment and a comparison group receiving placebo. Such study

designs are not possible when testing the efficacy of therapeutics for CFTR mutations that occur in a small number of people, or possibly even in a single person. N-of-1 clinical trial designs have been used in people with rare CFTR mutations to test the efficacy to CFTR modulators.<sup>31,67,93</sup> In N-of-1 clinical trials, an individual receives both placebo and a treatment, with a washout period in between, sometimes with multiple crossover events. In addition to testing CFTR modulator efficacy directly in human subjects, studies have used a variety of patient-derived cell lines, including rectal organoids<sup>93–97</sup> and respiratory epithelial cells,<sup>31,98–100</sup> to investigate individual response to CFTR modulators. In a unique move, the FDA expanded approval of CFTR modulators to rare CFTR mutations based on *in vitro* data alone, without clinical data.<sup>101</sup> Unfortunately, many rare mutations still have not been tested, leaving racial and ethnic minorities without access to modulator therapy.

### **Tobacco smoke exposure and CFTR modulator efficacy**

The benefit from CFTR modulators may be substantially less in people exposed to environmental tobacco smoke. A retrospective longitudinal analysis of data from the CF Foundation Patient Registry showed that tezacaftor/ivacaftor initiation showed that tezacaftor/ivacaftor users who were smoke-exposed had a lower baseline lung function and experienced a steeper lung function decline<sup>102</sup>. Over two years, the difference in ppFEV<sub>1</sub> by smoke exposure among tezacaftor/ivacaftor users increased by 1.2% (7.6% to 8.8%, p<0.001). In both mixed and fixed effects regression models, tezacaftor/ivacaftor use was associated with improved ppFEV<sub>1</sub> among unexposed individuals (1.2% and 1.7%, respectively; p<0.001 for both) but provided no benefit among smoke-exposed counterparts (0.3%, p=0.5 and 0.6%, p=0.07, respectively). These epidemiologic findings corroborate evidence from animal models and human studies that tobacco smoke exposure reduces CFTR functional expression,<sup>103–106</sup> likely through inhibiting anion transport by the CFTR.<sup>107–112</sup> The study results suggest that exposure to smoke may contribute to the observed heterogeneity of benefit from CFTR modulators, nullifying the effect of marginally effective therapies and reducing the benefit of the highly effective ones.<sup>113,114</sup>

The significance of these findings stem from the fact that approximately 20–30% of adults in the U.S. and E.U. use combustible tobacco products (varying by country) and usage is highest among those with lower educational status and household income.<sup>115,116</sup> Remarkably, the prevalence of tobacco use among parents of children with CF seems to be fairly similar to that of the general population.<sup>117,118</sup> The differential effect of CFTR drugs in smoke-exposed people with CF may exacerbate existing socioeconomic and racial and ethnic inequities in CF outcomes. Therefore, strategies and interventions to eliminate smoke exposure in CF households are critically needed for optimizing the effect of CFTR modulators, especially among racial/ethnic minorities and socioeconomically disadvantaged people.

### **Impact of CFTR modulators on health disparities**

The disparity in approval of and access to CFTR modulators in racial/ethnic minority patients will negatively impact already existing health inequities in CF. Even prior to CFTR modulators, racial and ethnic minorities had increased morbidity and mortality from CF compared to non-Hispanic White patients. These patients are more likely to be missed on

state newborn screening and be diagnosed later<sup>9,10</sup>. Hispanic patients with CF have an increased risk of mortality compared to non-Hispanic White patients and die at an earlier age.<sup>11–13</sup> Black patients with CF also have an increased risk of mortality compared to non-Hispanic White patients.<sup>13</sup> Both Hispanic and Black patients with CF have lower pulmonary function compared to non-Hispanic White patients.<sup>10,15–17</sup> Hispanic patients are at increased risk of acquiring pulmonary infections compared to non-Hispanic White patients and acquire infections at an earlier age.<sup>18,19</sup> Differences in morbidity or mortality have not yet been investigated specifically in Asian, Pacific Islander, Native American, or Native Alaskan patients, although one study found increased risk of mortality in children of minority race and ethnicity.<sup>14</sup>

As race and ethnicity are social constructs with little genetic basis,<sup>21–23</sup> it is essential to recognize that racial/ethnic disparities, including disparities in CF outcomes, are largely attributable to unequal social conditions and deeply rooted structural inequalities. For example, both Blacks and Hispanics with CF reside in neighborhoods with lower median household income<sup>24</sup> and have higher Medicaid coverage than non-Hispanic white counterparts.<sup>24</sup> Notably, disparities in CF outcomes by Hispanic ethnicity occur in spite of higher BMI and a larger proportion of residual function pancreatic sufficient CFTR mutations in the Hispanic population.<sup>106,20</sup> Understanding the racial/ethnic disparities in CF also requires careful consideration of the effects of psychosocial factors, health literacy and acculturation, and stress and racism. For example, African American and Hispanic patients report worse emotional and social functioning after controlling for disease severity and socioeconomic position.<sup>25</sup>

Existing racial and ethnic disparities in CF morbidity and mortality are likely to widen due to limited access to CFTR modulators among minority patients. To understand the causes and implications of disparate CF phenotypes in different racial/ethnic groups and to intervene in disease progression, it is critical to expand both bench research and research on the environmental and lifestyle factors that interact with genetically determined biological variables.

Providers who are anxious to obtain CFTR modulator therapy for patients not currently eligible face significant barriers. Most CF centers are not capable of real-time N-of-1 studies to check *in vitro* response to CFTR modulators. While there are research protocols at some centers throughout the country, these can be difficult for patients to enroll in, and when they do enroll, there are long delays to getting a result. Compassionate use programs through the pharmaceutical company have not been helpful for patients whose *CFTR* mutations have not been studied previously. Some CF centers report success with direct appeal to the insurance company for a clinical trial of 3–6 months to show clinical improvements in sweat chloride concentration, FEV<sub>1</sub>, and disease stability. Unfortunately, many insurance companies will not approve such a trial without evidence of an approved mutation.

## Conclusion and future directions

Even prior to the advent of CFTR modulators, non-White patients with CF face multiple barriers to achieving excellent outcomes from missed and late diagnosis to worse pulmonary

disease and increased mortality. Unequal access will only widen these disparities worldwide. There is not an easy answer to reaching equitable access to CFTR modulators, as barriers include rare uncharacterized *CFTR* mutations, no clear mechanism for testing efficacy of CFTR modulators in individuals, government approval or insurance approval, unaffordable costs, all leading to under-utilization of modulators in minority patients (Table 2). Nevertheless, finances and geographic location should not be determining what person with CF thrives or perishes due to access to CFTR modulators. Achieving equity will take significant work in research, clinical practice, and health policy. The CF community has made revolutionary, ground-breaking progress in the treatment of CF. This same energy and dedication is now needed to absolve health disparities in CF.

## References

1. Cystic Fibrosis Foundation Patient Registry 2019 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation;2020.
2. Oates GR, Schechter MS. Socioeconomic status and health outcomes: cystic fibrosis as a model. Expert review of respiratory medicine. 2016;10(9):967–977. [PubMed: 27268142]
3. Schechter MS, Shelton BJ, Margolis PA, FitzSimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. American journal of respiratory and critical care medicine. 2001;163(6):1331–1337. [PubMed: 11371397]
4. Oates GR, Baker E, Rowe SM, et al. Tobacco smoke exposure and socioeconomic factors are independent predictors of pulmonary decline in pediatric cystic fibrosis. Journal of Cystic Fibrosis. 2020;19(5):783–790. [PubMed: 32081643]
5. O'Connor GT, Quinton HB, Kneeland T, et al. Median household income and mortality rate in cystic fibrosis. Pediatrics. 2003;111(4):e333–e339. [PubMed: 12671148]
6. Barr HL, Britton J, Smyth AR, Fogarty AW. Association between socioeconomic status, sex, and age at death from cystic fibrosis in England and Wales (1959 to 2008): cross sectional study. Bmj. 2011;343.
7. Schrijver I, Pique L, Graham S, Pearl M, Cherry A, Kharrazi M. The spectrum of CFTR variants in nonwhite cystic fibrosis patients: implications for molecular diagnostic testing. The Journal of Molecular Diagnostics. 2016;18(1):39–50. [PubMed: 26708955]
8. Pique L, Graham S, Pearl M, Kharrazi M, Schrijver I. Cystic fibrosis newborn screening programs: implications of the CFTR variant spectrum in nonwhite patients. Genetics in Medicine. 2017;19(1):36. [PubMed: 27148940]
9. Watts KD, Layne B, Harris A, McColley SA. Hispanic infants with cystic fibrosis show low CFTR mutation detection rates in the Illinois newborn screening program. Journal of genetic counseling. 2012;21(5):671–675. [PubMed: 22311127]
10. McGarry ME, Neuhaus J, Nielson DW, Burchard EG, Ly NP. Pulmonary function disparities exist and persist in Hispanic patients with cystic fibrosis: A longitudinal analysis. Pediatric pulmonology. 2017;52(12):1550–1557. [PubMed: 29082671]
11. Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH. Assessing differences in mortality rates and risk factors between Hispanic and non-Hispanic patients with cystic fibrosis in California. CHEST Journal. 2016;149(2):380–389.
12. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R. Disparities in Mortality of Hispanic Cystic Fibrosis Patients in the United States: A National and Regional Cohort Study. American journal of respiratory and critical care medicine. 2018(ja).
13. O'Connor GT, Quinton HB, Kahn R, et al. Case-mix adjustment for evaluation of mortality in cystic fibrosis. Pediatric pulmonology. 2002;33(2):99–105. [PubMed: 11802245]
14. McColley SA, Schechter MS, Morgan WJ, Pasta DJ, Craib ML, Konstan MW. Risk factors for mortality before age 18 years in cystic fibrosis. Pediatric pulmonology. 2017;52(7):909–915. [PubMed: 28436621]

15. McGarry ME, Neuhaus JM, Nielson DW, Ly NP. Regional variations in longitudinal pulmonary function: A comparison of Hispanic and non-Hispanic subjects with cystic fibrosis in the United States. *Pediatric pulmonology*. 2019.
16. Hamosh A, FitzSimmons SC, Macek M Jr, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *The Journal of pediatrics*. 1998;132(2):255–259. [PubMed: 9506637]
17. Hamosh A, FitzSimmons SC, Macek M Jr., Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *J Pediatr*. 1998;132(2):255–259. [PubMed: 9506637]
18. McGarry ME, Huang C-Y, Nielson DW, Ly NP. Early acquisition and conversion of *Pseudomonas aeruginosa* in Hispanic youth with cystic fibrosis in the United States. *Journal of Cystic Fibrosis*. 2021;20(3):424–431. [PubMed: 33162303]
19. Sawicki GS, Van Brunt K, Booth J, et al. Disease burden in people with cystic fibrosis heterozygous for F508del and a minimal function mutation. *Journal of Cystic Fibrosis*. 2021.
20. Watts KD, Seshadri R, Sullivan C, McColley SA. Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population. *Pediatr Pulmonol*. 2009;44(6):594–601. [PubMed: 19437506]
21. Caldwell SH, Popenoe R. Perceptions and misperceptions of skin color. *Ann Intern Med*. 1995;122(8):614–617. [PubMed: 7887557]
22. Kahn J How a drug becomes “ethnic”: law, commerce, and the production of racial categories in medicine. *Yale J Health Policy Law Ethics*. 2004;4(1):1–46. [PubMed: 15052858]
23. Hoover EL. There is no scientific rationale for race-based research. *J Natl Med Assoc*. 2007;99(6):690–692. [PubMed: 17595942]
24. Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH. Assessing Differences in Mortality Rates and Risk Factors Between Hispanic and Non-Hispanic Patients With Cystic Fibrosis in California. *Chest*. 2016;149(2):380–389. [PubMed: 26086984]
25. Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. *Chest*. 2010;137(3):642–650. [PubMed: 19820076]
26. Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. *The Lancet Respiratory Medicine*. 2020;8(1):65–124. [PubMed: 31570318]
27. The Clinical and Functional TRanslation of CFTR (CFTR2); available at <http://cftr2.org>. Accessed 10/12/2021, 2021.
28. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. *The Lancet Respiratory Medicine*. 2016;4(8):662–674. [PubMed: 27053340]
29. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *New England Journal of Medicine*. 2011;365(18):1663–1672. [PubMed: 22047557]
30. McGarry ME, Nielson DW. Normalization of sweat chloride concentration and clinical improvement with ivacaftor in a patient with cystic fibrosis with mutation S549N. *CHEST Journal*. 2013;144(4):1376–1378.
31. McGarry ME, Illek B, Ly NP, et al. In vivo and in vitro ivacaftor response in cystic fibrosis patients with residual CFTR function: N-of-1 studies. *Pediatric pulmonology*. 2017;52(4):472–479. [PubMed: 28068001]
32. Yarlagadda S, Zhang W, Penmatsa H, et al. A young Hispanic with c. 1646G>A mutation exhibits severe cystic fibrosis lung disease: is ivacaftor an option for therapy? *American journal of respiratory and critical care medicine*. 2012;186(7):694–696. [PubMed: 23027855]
33. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *Journal of Cystic Fibrosis*. 2014;13(6):674–680. [PubMed: 25266159]
34. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *The Lancet Respiratory Medicine*. 2015;3(7):524–533. [PubMed: 26070913]
35. Cystic Fibrosis Foundation Patient Registry, 2019 Annual Data Report Bethesda, Maryland.

36. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *New England Journal of Medicine*. 2015;373(3):220–231. [PubMed: 25981758]
37. Elborn JS, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis. *The Lancet Respiratory Medicine*. 2016;4(8):617–626. [PubMed: 27298017]
38. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *New England Journal of Medicine*. 2017;377(21):2013–2023. [PubMed: 29099344]
39. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor–ivacaftor in residual-function heterozygotes with cystic fibrosis. *New England Journal of Medicine*. 2017;377(21):2024–2035. [PubMed: 29099333]
40. Donaldson SH, Pilewski JM, Griese M, et al. Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American journal of respiratory and critical care medicine*. 2018;197(2):214–224. [PubMed: 28930490]
41. McColley SA, Konstan MW, Ramsey BW, et al. Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1. *Journal of Cystic Fibrosis*. 2019;18(1):94–101. [PubMed: 30146268]
42. Keating D, Marigowda G, Burr L, et al. VX-445–tezacaftor–ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *New England Journal of Medicine*. 2018;379(17):1612–1620. [PubMed: 30334692]
43. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *American journal of Diseases of Children*. 1938;56(2):344–399.
44. Bell SC, Mall MA, Gutierrez H, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med*. 2020;8(1):65–124. [PubMed: 31570318]
45. Pérez MM, Luna MC, Pivetta OH, Keyeux G. CFTR gene analysis in Latin American CF patients: heterogeneous origin and distribution of mutations across the continent. *Journal of Cystic Fibrosis*. 2007;6(3):194–208. [PubMed: 16963320]
46. Sugarman EA, Rohlf s EM, Silverman LM, Allitto BA. CFTR mutation distribution among US Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations. *Genetics in Medicine*. 2004;6(5):392–399. [PubMed: 15371903]
47. Organization WH. The molecular genetic epidemiology of cystic fibrosis. 1983.
48. Zeiger AM, McGarry ME, Mak AC, et al. Identification of CFTR variants in Latino patients with cystic fibrosis from the Dominican Republic and Puerto Rico. *Pediatric pulmonology*. 2020;55(2):533–540. [PubMed: 31665830]
49. McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatric Pulmonology*. 2021;56(6):1496–1503. [PubMed: 33470563]
50. Ross LF. Newborn screening for cystic fibrosis: a lesson in public health disparities. *J Pediatr*. 2008;153(3):308–313. [PubMed: 18718257]
51. Sawicki GS, Dasenbrook E, Fink AK, Schechter MS. Rate of uptake of ivacaftor use after US Food and Drug Administration approval among patients enrolled in the US Cystic Fibrosis Foundation Patient Registry. *Annals of the American Thoracic Society*. 2015;12(8):1146–1152. [PubMed: 26073026]
52. Sawicki GS, Fink AK, Schechter MS, Loeffler DR, Mayer-Hamblett N. Rate and predictors of prescription of lumacaftor–Ivacaftor in the 18 months following approval in the United States. *Journal of Cystic Fibrosis*. 2018;17(6):742–746. [PubMed: 30201329]
53. McGarry ME, McColley SA. Minorities are underrepresented in clinical trials of pharmaceutical agents for cystic fibrosis. *Annals of the American Thoracic Society*. 2016;13(10):1721–1725. [PubMed: 27410177]
54. Goyal MK, Johnson TJ, Chamberlain JM, et al. Racial and ethnic differences in antibiotic use for viral illness in emergency departments. *Pediatrics*. 2017;140(4).

55. Gerber JS, Prasad PA, Localio AR, et al. Racial differences in antibiotic prescribing by primary care pediatricians. *Pediatrics*. 2013;131(4):677–684. [PubMed: 23509168]
56. Goyal MK, Kuppermann N, Cleary SD, Teach SJ, Chamberlain JM. Racial disparities in pain management of children with appendicitis in emergency departments. *JAMA pediatrics*. 2015;169(11):996–1002. [PubMed: 26366984]
57. Briesacher B, Limcangco R, Gaskin D. Racial and ethnic disparities in prescription coverage and medication use. *Health care financing review*. 2003;25(2):63. [PubMed: 15124378]
58. Huang ES, Brown SE, Thakur N, et al. Racial/ethnic differences in concerns about current and future medications among patients with type 2 diabetes. *Diabetes care*. 2009;32(2):311–316. [PubMed: 19017766]
59. Schechter MS, McColley SA, Silva S, et al. Association of socioeconomic status with the use of chronic therapies and healthcare utilization in children with cystic fibrosis. *The Journal of pediatrics*. 2009;155(5):634–639. e634.
60. DiGirolamo M, Kang L, Schechter M. QI-INDUCED IMPROVEMENTS MAY LEAD TO A REDUCTION OF SOCIOECONOMIC DISPARITIES IN CF HEALTH OUTCOMES. Paper presented at: PEDIATRIC PULMONOLOGY 2020.
61. O’Sullivan BP, Orenstein DM, Milla CE. Pricing for orphan drugs: will the market bear what society cannot? *Jama*. 2013;310(13):1343–1344. [PubMed: 24084916]
62. Pollack AOrkambi, a new cystic fibrosis drug, wins FDA approval. *New York Times* <http://www.nytimes.com/2015/07/03/business/orkambi-a-new-cystic-fibrosis-drug-wins-fda-approval.html>. 2015.
63. Ferkol T, Quinton P. Precision medicine: at what price? In: American Thoracic Society; 2015.
64. Balk E, Trikalinos T, Kuntz K, et al. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary. Boston, MA: Institute for Clinical and Economic Review; June 7, 2018 2018.
65. Marson FAL. Cost of precision medicine at a referral center for cystic fibrosis. *Jornal Brasileiro de Pneumologia*. 2020;46.
66. Vertex, Our Approved Medicines. <https://global.vrtx.com/medicines>. Accessed 10/13/2021.
67. Nick JA, Clair CS, Jones MC, Lan L, Higgins M, Team V--S. Ivacaftor in cystic fibrosis with residual function: Lung function results from an N-of-1 study. *Journal of Cystic Fibrosis*. 2020;19(1):91–98. [PubMed: 31784217]
68. Davies JC, Wainwright CE, Sawicki GS, et al. Ivacaftor in infants aged 4 to < 12 months with cystic fibrosis and a gating mutation. Results of a two-part phase 3 clinical trial. *American journal of respiratory and critical care medicine*. 2021;203(5):585–593. [PubMed: 33023304]
69. Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWD): an open-label, single-arm study. *The Lancet Respiratory Medicine*. 2016;4(2):107–115. [PubMed: 26803277]
70. Pilewski JM, De Boeck K, Nick JA, et al. Long-Term Ivacaftor in People Aged 6 Years and Older with Cystic Fibrosis with Ivacaftor-Responsive Mutations. *Pulmonary therapy*. 2020;6(2):303–313. [PubMed: 32965659]
71. Rosenfeld M, Cunningham S, Harris WT, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2–5 years (KLIMB). *Journal of Cystic Fibrosis*. 2019;18(6):838–843. [PubMed: 31053538]
72. Guimbello J, Baines A, Paynter A, et al. Long term clinical effectiveness of ivacaftor in people with the G551D CFTR mutation. *Journal of Cystic Fibrosis*. 2021;20(2):213–219. [PubMed: 33249004]
73. Guimbello J, Solomon GM, Baines A, et al. Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *Journal of Cystic Fibrosis*. 2019;18(1):102–109. [PubMed: 29685811]
74. Hoppe JE, Chilvers M, Ratjen F, et al. Long-term safety of lumacaftor–ivacaftor in children aged 2–5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. *The Lancet Respiratory Medicine*. 2021.

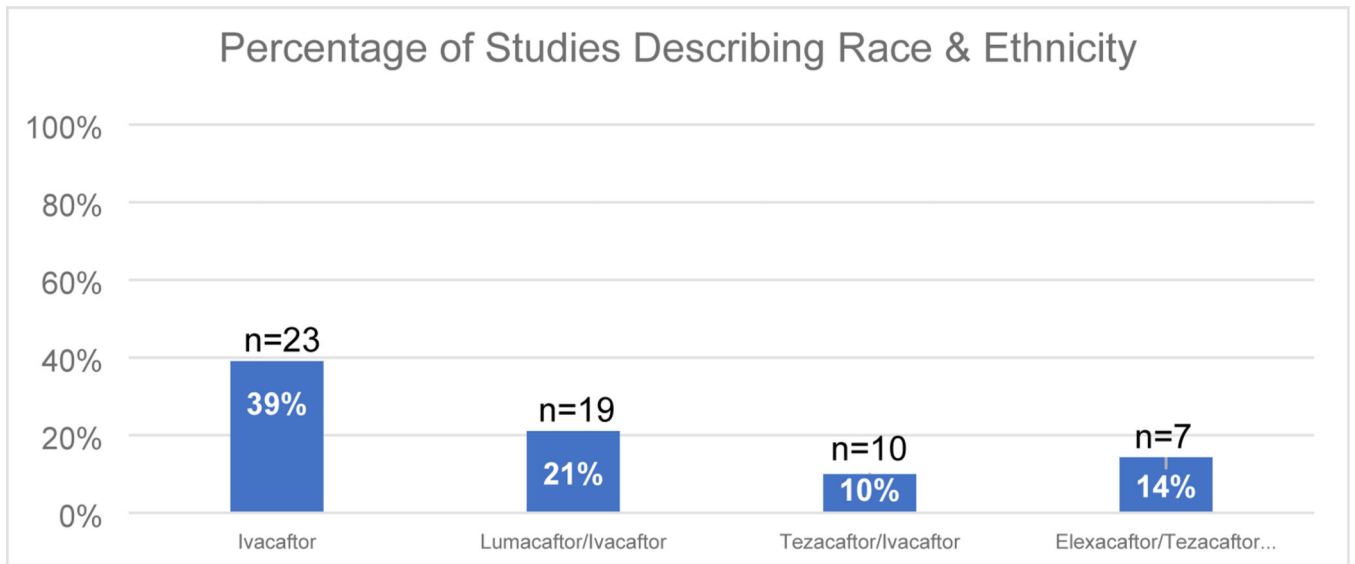
75. Berkers G, van der Meer R, Heijerman H, et al. Lumacaftor/ivacaftor in people with cystic fibrosis with an A455E–CFTR mutation. *Journal of Cystic Fibrosis*. 2020.
76. Sagel SD, Khan U, Heltshe SL, et al. Clinical effectiveness of lumacaftor/ivacaftor in patients with cystic fibrosis homozygous for F508del-CFTR. *A Clinical Trial. Annals of the American Thoracic Society*. 2021;18(1):75–83. [PubMed: 32644818]
77. Flume PA, Biner RF, Downey DG, et al. Long-term safety and efficacy of tezacaftor–ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study. *The Lancet Respiratory Medicine*. 2021.
78. Schwarz C, Sutharsan S, Epaud R, et al. Tezacaftor/ivacaftor in people with cystic fibrosis who stopped lumacaftor/ivacaftor due to respiratory adverse events. *Journal of Cystic Fibrosis*. 2021;20(2):228–233. [PubMed: 32586736]
79. Davies JC, Sermet-Gaudelus I, Naehrlich L, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *Journal of Cystic Fibrosis*. 2021;20(1):68–77. [PubMed: 32967799]
80. Walker S, Flume P, McNamara J, et al. A phase 3 study of tezacaftor in combination with ivacaftor in children aged 6 through 11 years with cystic fibrosis. *Journal of Cystic Fibrosis*. 2019;18(5):708–713. [PubMed: 31253540]
81. McKone EF, DiMango EA, Sutharsan S, et al. A phase 3, randomized, double-blind, parallel-group study to evaluate tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating mutation. *Journal of Cystic Fibrosis*. 2021;20(2):234–242. [PubMed: 33339768]
82. Middleton PG, Mall MA, D evínek P, et al. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *New England Journal of Medicine*. 2019;381(19):1809–1819. [PubMed: 31697873]
83. Burgel P-R, Durieu I, Chiron R, et al. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *American Journal of Respiratory and Critical Care Medicine*. 2021(ja).
84. Heijerman HG, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet*. 2019;394(10212):1940–1948.
85. Djavid AR, Thompson AE, Irace AL, et al. Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Advanced Cystic Fibrosis Lung Disease. *Annals of the American Thoracic Society*. 2021(ja).
86. DiMango E, Overdeest J, Keating C, Francis SF, Dansky D, Gudis D. Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis. *Journal of Cystic Fibrosis*. 2021;20(3):460–463. [PubMed: 32694034]
87. Barry PJ, Mall MA, Álvarez A, et al. Triple Therapy for Cystic Fibrosis Phe508del–Gating and–Residual Function Genotypes. *New England Journal of Medicine*. 2021;385(9):815–825. [PubMed: 34437784]
88. Transparency McGarry M. and Diversity In Cystic Fibrosis Research. *Lancet*. 2020;396(10251):601.
89. McGarry ME. Triple Therapy for Cystic Fibrosis with a Phe508del CFTR Mutation. *The New England Journal of Medicine*. 2020;382(7):684–684.
90. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS medicine*. 2006;3(2):e19. [PubMed: 16318411]
91. NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research. [https://grants.nih.gov/grants/funding/women\\_min/guidelines.htm](https://grants.nih.gov/grants/funding/women_min/guidelines.htm). Accessed 05/08/2019, 2019.
92. Flanagan A, Frey T, Christiansen SL, Committee AMoS. Updated guidance on the reporting of race and ethnicity in medical and science journals. *Jama*. 2021;326(7):621–627. [PubMed: 34402850]

93. Kerem E, Cohen-Cymbarknoh M, Tsabari R, et al. Ivacaftor in people with cystic fibrosis and a 3849+ 10kb C→T or D1152H residual function mutation. *Annals of the American Thoracic Society*. 2021;18(3):433–441. [PubMed: 33095038]
94. Dekkers JF, Berkers G, Kruisselbrink E, et al. Characterizing responses to CFTRmodulating drugs using rectal organoids derived from subjects with cystic fibrosis. *Science translational medicine*. 2016;8(344):344ra384–344ra384.
95. Graeber SY, van Mourik P, Vonk AM, et al. Comparison of Organoid Swelling and In Vivo Biomarkers of CFTR Function to Determine Effects of Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for the F508del Mutation. *American Journal of Respiratory and Critical Care Medicine*. 2020;202(11):1589–1592. [PubMed: 32687398]
96. Berkers G, van Mourik P, Vonk AM, et al. Rectal organoids enable personalized treatment of cystic fibrosis. *Cell reports*. 2019;26(7):1701–1708. e1703.
97. Furstova E, Dousova T, Beranek J, et al. Response to elxacaftor/tezacaftor/ivacaftor in intestinal organoids derived from people with cystic fibrosis. *Journal of Cystic Fibrosis*. 2021.
98. Debley JS, Barrow KA, Rich LM, Singh P, McKone EF, Nichols DP. Correlation between Ivacaftor-induced CFTR activation in airway epithelial cells and improved lung function: a Proof-of-Concept study. *Annals of the American Thoracic Society*. 2020;17(8):1024–1027. [PubMed: 32421352]
99. Silva IA, Railean V, Duarte A, Amaral MD. Personalized Medicine Based on Nasal Epithelial Cells: Comparative Studies with Rectal Biopsies and Intestinal Organoids. *Journal of Personalized Medicine*. 2021;11(5):421. [PubMed: 34065744]
100. Pranke IM, Hatton A, Simonin J, et al. Correction of CFTR function in nasal epithelial cells from cystic fibrosis patients predicts improvement of respiratory function by CFTR modulators. *Scientific reports*. 2017;7(1):1–11. [PubMed: 28127051]
101. Durmowicz AG, Lim R, Rogers H, Rosebraugh CJ, Chowdhury BA. The US Food and Drug Administration’s experience with ivacaftor in cystic fibrosis. Establishing efficacy using in vitro data in lieu of a clinical trial. *Annals of the American Thoracic Society*. 2018;15(1):1–2. [PubMed: 29020455]
102. Baker E, Harris WT, Rowe SM, Rutland SB, Oates GR. Tobacco smoke exposure limits the therapeutic benefit of tezacaftor/ivacaftor in pediatric patients with cystic fibrosis. *Journal of Cystic Fibrosis*. 2021;20(4):612–617. [PubMed: 33023836]
103. Raju SV, Rasmussen L, Sloane PA, Tang LP, Libby EF, Rowe SM. Roflumilast reverses CFTR-mediated ion transport dysfunction in cigarette smoke-exposed mice. *Respir Res*. 2017;18(1):173. [PubMed: 28923049]
104. Rab A, Rowe SM, Raju SV, Bebok Z, Matalon S, Collawn JF. Cigarette smoke and CFTR: implications in the pathogenesis of COPD. *American journal of physiology Lung cellular and molecular physiology*. 2013;305(8):L530–541. [PubMed: 23934925]
105. Rasmussen JE, Sheridan JT, Polk W, Davies CM, Tarran R. Cigarette smoke-induced Ca<sup>2+</sup> release leads to cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction. *The Journal of biological chemistry*. 2014;289(11):7671–7681. [PubMed: 24448802]
106. Raju SV, Jackson PL, Courville CA, et al. Cigarette smoke induces systemic defects in cystic fibrosis transmembrane conductance regulator function. *Am J Respir Crit Care Med*. 2013;188(11):1321–1330. [PubMed: 24040746]
107. Sloane PA, Shastry S, Wilhelm A, et al. A pharmacologic approach to acquired cystic fibrosis transmembrane conductance regulator dysfunction in smoking related lung disease. *PLoS ONE*. 2012;7(6):e39809.
108. Cantin AM, Hanrahan JW, Bilodeau G, et al. Cystic fibrosis transmembrane conductance regulator function is suppressed in cigarette smokers. *Am J Respir Crit Care Med*. 2006;173(10):1139–1144. [PubMed: 16497995]
109. Kreindler JL, Jackson AD, Kemp PA, Bridges RJ, Danahay H. Inhibition of chloride secretion in human bronchial epithelial cells by cigarette smoke extract. *Am J Physiol Lung Cell Mol Physiol*. 2005;288(5):L894–902. [PubMed: 15626749]

110. Clunes LA, Davies CM, Coakley RD, et al. Cigarette smoke exposure induces CFTR internalization and insolubility, leading to airway surface liquid dehydration. *Faseb J*. 2012;26(2):533–545. [PubMed: 21990373]
111. Savitski AN, Mesaros C, Blair IA, Cohen NA, Kreindler JL. Secondhand smoke inhibits both Cl<sup>-</sup> and K<sup>+</sup> conductances in normal human bronchial epithelial cells. *Respir Res*. 2009;10:120. [PubMed: 19943936]
112. Lin VY, Fain MD, Jackson PL, et al. Vaporized E-Cigarette Liquids Induce Ion Transport Dysfunction in Airway Epithelia. *Am J Respir Cell Mol Biol*. 2019;61(2):162–173. [PubMed: 30576219]
113. Taylor-Cousar J, Niknian M, Gilmartin G, Pilewski JM, investigators VX. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: Safety and efficacy in an expanded access program in the United States. *J Cyst Fibros*. 2016;15(1):116–122. [PubMed: 25682022]
114. Hebestreit H, Sauer-Heilborn A, Fischer R, Kading M, Mainz JG. Effects of ivacaftor on severely ill patients with cystic fibrosis carrying a G551D mutation. *J Cyst Fibros*. 2013;12(6):599–603. [PubMed: 23757359]
115. Gallus S, Lugo A, Liu X, et al. Who smokes in Europe? Data from 12 European countries in the TackSHS survey (2017–2018). *Journal of epidemiology*. 2020:JE20190344.
116. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults—United States, 2019. *Morbidity and Mortality Weekly Report*. 2020;69(46):1736. [PubMed: 33211681]
117. Ong T, Schechter M, Yang J, et al. Socioeconomic Status, Smoke Exposure, and Health Outcomes in Young Children With Cystic Fibrosis. *Pediatrics*. 2017;139(2).
118. Oates GR, Baker E, Rowe SM, et al. Tobacco smoke exposure and socioeconomic factors are independent predictors of pulmonary decline in pediatric cystic fibrosis. *J Cyst Fibros*. 2020.

**Educational Aims:****The reader will come to appreciate that:**

- Newborn screening methodologies may underserve minorities with less common genotypes, delay diagnosis and perpetuate poorer CF health outcomes.
- The lack of inclusion of racial/ethnic minorities in clinical trials of CFTR modulators has implications for adverse events, drug metabolism and therapeutic response.
- The cost of modulator therapy could be more than US\$15 million over the life of an individual.
- People with CF in Eastern Europe, Asia, Africa, and most of South America have restricted access to CFTR modulators.



**Figure 1:**  
Percentage of CFTR Modulator Studies Describing Subject Race and Ethnicity

**Table 1:**

## Countries with Branded CFTR Modulator Market Authorization

All 4 CFTR modulators	Ivacaftor, Lumacaftor/ivacaftor, Tezacaftor/ivacaftor	Lumacaftor/ivacaftor
<ul style="list-style-type: none"><li>• Australia</li><li>• Canada</li><li>• European Union countries</li><li>• Iceland</li><li>• Israel</li><li>• Liechtenstein</li><li>• Norway</li><li>• Switzerland</li><li>• United Kingdom</li><li>• United States</li></ul>	<ul style="list-style-type: none"><li>• Brazil</li></ul>	<ul style="list-style-type: none"><li>• Russia</li></ul>

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 2.**

## Barriers to and solutions for CFTR modulator equity

Type	Potential Barriers	Possible Solutions
Genetics	Incomplete <i>CFTR</i> genotyping: only one or no mutations identified	Further research in genetics of CF, full sequencing of patients without 2 mutations
	Rare and novel mutations not eligible for clinical trials	Therotyping, N-of-1 clinical trials, grants to fund research
Clinical trials	Minorities not included in clinical trials even when qualify	Adopt NIH policy across all CFTR trials to ensure equal representation
	No standard pathway for testing efficacy in <i>CFTR</i> mutations not previously investigated	Increased research, consensus guidelines needed
Public policy	No approval of CFTR modulators for all mutations in which they have shown efficacy	Increased advocacy for approval
	Newborn screening methodologies tailored primarily to non-Hispanic Whites	Develop newborn screening methodologies suitable for minorities
Financial	Cost to healthcare system; unaffordable for smaller or lower-income countries	Negotiate affordable options with pharmaceutical companies
	Inconsistent coverage across health insurance plans	Negotiate with policy makers and insurance providers for coverage
Health care	CFTR modulators under-prescribed to minority patients	Provide education and implicit bias training to CF providers
	CFTR modulators declined by minority patients	Interventions to address concerns, develop trust
Environmental	Reduced benefit of CFTR modulators due to disproportionate smoke exposure in racial/ethnic minorities	Smoking cessation and exposure prevention interventions tailored to racial/ethnic minorities