Representation of Minoritized People with Cystic Fibrosis in CF Therapeutics Development Network Clinical Studies

Tijana Milinic

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Science

University of Washington
2025

Committee:
Susan R. Heckbert

Christopher H. Goss

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Representation of Minoritized People with Cystic Fibrosis in CF Therapeutics Development Network Clinical Studies

Tijana Milinic

Chair of the Supervisory Committee:

Susan R. Heckbert

Department of Epidemiology

Black and Hispanic people with CF (PwCF) experience a greater burden of worse health outcomes related to pulmonary disease compared to White, non-Hispanic PwCF. Prior evidence suggests that these communities are underrepresented in clinical research in CF. We used clinical study data from four recent modulator studies (CHEC-SC, PROMISE, PROSPECT, and GOAL) as well as CF Foundation Patient Registry data on persons seen at the same centers while these studies were enrolling. We selected potential registry controls who had not enrolled into studies but were otherwise eligible based on inclusion and exclusion criteria. We assessed rates of study enrollment separately for Black race and Hispanic ethnicity versus non-Hispanic White PwCF as a reference. We used propensity weighted Poisson regression models to account for potential confounders in the relationship between race and study participation. This study analyzed the enrollment characteristics of 3,594 persons in modulator studies and compared them with 14,888 eligible individuals based on CFF Patient Registry data. Enrollees were younger (median age 19 years) and more likely to have at least three baseline visits and live within 30 miles of the study site. Multivariable analysis revealed racial/ethnic disparities in enrollment. Black individuals were significantly less likely than non-Hispanic White individuals to enroll in CHEC-SC and PROMISE, with a 17% and 32% lower likelihood, respectively. Hispanic individuals had lower enrollment in PROMISE but higher enrollment in PROSPECT. The differences in enrollment rates were stronger at sites with fewer minority participants. These results suggest that Black and Hispanic PwCF are significantly less likely to be included in CF clinical research than White PwCF. Future research will include analysis of multiple CF clinical studies to evaluate if this relationship is upheld in studies with varying inclusion/ exclusion criteria and clinical sites.

Background:

Clinical trials in cystic fibrosis (CF) have led to dramatic advancements in CF therapeutics and clinical care that have substantially improved survival and morbidity in CF related lung disease(1, 2). Engaging in clinical research has offered significant benefits for individuals with CF. Participants in new drug studies, such as those studying the effects of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, gain access to life prolonging therapies years ahead of the general population (3). Beyond this, clinical trials are vital in evaluating the efficacy of new therapies, identifying adverse effects, and expanding understanding of disease processes.

A comparison of CF clinical study participants to an overall population provided in the CF Foundation (CFF) Patient Registry showed that research participation in CF is high, with an overall estimated 30% participation rate(4). Importantly, this 2006 study by Goss et al. showed that research participants were more likely to have private insurance and to identify as White. Between 1999 and 2015, approximately 80% of CF pharmacology clinical trials did not describe race or ethnicity of participants(5). Among studies where race and ethnicity data were reported, 94.4% of study participants were identified as White race and 24.4% of studies included no minoritized PwCF. More recently, a 2023 single center study found that 35.9% of non-Hispanic White PwCF participated in onsite clinical trials while 21% of PwCF identifying with racial and ethnically minoritized groups participated in onsite studies(6). This study found that no racially or ethnically minoritized PwCF participated in off-site clinical trials. Despite clinical research being extremely important to advance clinical outcomes and provide access to therapies, there is clear evidence for lack of equitable enrollment in clinical studies for minoritized PwCF.

In 2022, 8.8% of PwCF in the CFF Patient Registry Annual Report were identified as race other than White and 10.0% of individuals identified as Hispanic ethnicity (1). Although Black and Hispanic individuals make up an increasing share of the cystic fibrosis (CF) population, they face greater health challenges associated with the condition. This includes poorer nutritional status and reduced lung function among Black CF patients, a threefold higher risk of mortality among Hispanic patients, and an increased likelihood of acquiring pulmonary infections at a younger age in Hispanic patients(7–10). Lack of representation in clinical studies compounds these existing inequities.

This study evaluated the equity of racial and ethnic representation in CF modulator studies in the CF Therapeutics Development Network (CF TDN), a large clinical trial network comprised of over 90 study sites conducting more than 120 observational and interventional studies since 1998. Our study compares participation by race and ethnicity in CF TDN studies to an overall population available in the CFF Patient Registry.

Methods:

Study Population and Data Sources

Study eligible PwCF were identified using data from the CFF Patient Registry which captures encounter based clinical data for approximately 85% of the US CF population(11). We used study data from the CF TDN, merging study data from four large, recent observational studies, including Characterizing CFTR Modulated Changes in Sweat Chloride and their Association with Clinical Outcomes (NCT 03350828) (CHEC-SC); A Prospective Study to Evaluate Biological and

Clinical Effects of Significantly Corrected CFTR Function (PROMISE) (NCT04038047); Prospective Longitudinal Study of CFTR-dependent Disease Profiling in CF (PROSPECT), and the G551D Observational Study (GOAL) (NCT 01521338) (see Supplemental Table e1 for study characteristics and eligibility criteria) (12–15). To identify factors associated with study participation, we identified persons eligible for each study based on inclusion and exclusion criteria from CFF Patient Registry captured during the years of each study's accrual. For participants in the four studies, we captured CFF Patient Registry data from the year of enrollment. For eligible persons who did not enroll, we randomly selected CFF Patient Registry data from one of the years in which they were eligible for the study. Persons eligible for more than one study were included in the evaluation of the most recent study. Baseline data reported corresponds to year of enrollment for enrolled PwCF and random year selected and eligible for those who did not enroll. The study was approved by the University of Washington Institutional Review Board (STUDY00004003).

Statistical Analyses

We captured race from the CFFPR, entered through a combination of self-reported and staff entered data with pre-specified, fixed categories. We followed precedent by McGarry and McColley and categorized people based on a combination of race and ethnicity (5, 16). We compared enrollment of PwCF identified as either Hispanic ethnicity, non-Hispanic Black race, or non-Hispanic White race.

To identify whether race was associated with study participation in a causal way, we constructed a causal inference diagram to identify potential confounders and to distinguish them from mediators and other relationships (Figure 1). Using Daggity, we determined that bias in identifying the direct, causal association of race with study participation could be minimized by adjusting for these measures: demographics, lung function as measured by percent predicted forced expiratory volume in one second (ppFEV1), CFTR genotype, socioeconomic status, CF related diabetes status, visit frequency, and exacerbation frequency(17, 18). Socioeconomic status variables included highest education level of patient and patient's parents, employment, and insurance type. Distance to study center as calculated using zip code was additionally included. We approximated distance from individual residences to study sites by computing the distance between the latitude and longitude at the centroid of each zip code. We used the software python, pgeocode package, which pulls zipcode information from the GeoNames database (19, 20). In regression, the distances were categorized as: <=30 miles, 31 to 60 miles, and >60 miles. For each study separately, we constructed logistic regression models with race or ethnicity as the outcome and including the above listed covariates, building the propensity for the exposure of interest (race or ethnicity). We built propensity scores separately for Black race versus non-Hispanic White race, and then for Hispanic ethnicity versus non-Hispanic White race.

Weighting on these propensity scores to control for confounding, we then performed Poisson regressions on the outcome of interest (study participation)(21). The exposure of interest was the only fixed effect. Study site number was included as a random effect, as well as inverse weighting on propensity of the exposure. Inverse probability weighting equalizes the groups of different races or ethnicities over all included confounders and serves to make the groups of different races or ethnicities *otherwise* comparable for "risk" of the outcome (study participation).

Poisson regression provides effect estimates in a more interpretable format than logistic regression: risk ratios instead of odds ratios. In these analyses, we excluded sites for whom no persons of that race/ethnicity were reported in the CFF Patient Registry (where the probability of enrolling a person of minoritized race/ethnicity was zero). Because inclusion and exclusion criteria varied between studies and different sites enrolled in each, we analyzed each study separately (see Supplemental Table e1). Analyses were conducted using R software (R version 4.4.3).

While the random term for site permits differences in enrollment rates geographically, we also wondered whether the number of persons of minoritized race or ethnicity in the site catchment area (eligible persons) might be related to any observed differences by race or ethnicity. Therefore, we additionally assessed whether any association between race/ethnicity and enrollment frequency might depend on the number of eligible persons of the race/ethnicity of interest. We did this using interaction terms between the race of the eligible CFFPR registrant and a categorical variable for number of persons of that race/ethnicity at that site. We used tertiles to determine categories for numbers of persons of that race/ethnicity.

Results:

Cohort Characteristics

We identified 3,594 persons who were enrolled into modulator studies, either CHEC-SC, PROMISE, PROSPECT, or GOAL and who also had CFF Patient Registry data collected in the same year. We also identified 14,888 persons who were eligible for at least one study based on CFF Patient Registry data during the time of the studies. Characteristics of the persons enrolled and persons eligible but not enrolled are shown in Table 1. Median age for those enrolled in modular studies was 19 years versus 25 years for those not enrolled. A greater proportion of those enrolled in modulator studies had at least three annual visits at baseline (82% enrollees versus 54% those not enrolled) and lived within 30 miles of the study site (51% those enrolled versus 36% those not enrolled). Information about the distribution of the number and proportion of Black and Hispanic PwCF at the CFFPR sites is shown in Tables 2a and 2b. The associations of characteristics with Black race and with Hispanic ethnicity as computed for the propensity scores are shown in Supplemental Tables e2 and e3. In regression, 8% of persons could not be included due to missing data: 3% of persons had unknown ethnicity, 4% had unknown BMI, and 1% had unknown values for each of diabetes at baseline, visits in the current year, and zip code. As 13% of persons had unknown FEV, those persons were retained in analyses and a category for missing FEV was created.

Multivariable Analyses

After adjustment for measured confounders using inverse weighting in the Poisson regression analysis, Black persons were 17% less likely than White persons to be enrolled in CHEC-SC (RR=0.83, 95% CI 0.77, 0.90; Table 3a) and 32% less likely to be enrolled in PROMISE (RR=0.68 95% CI 0.57 to 0.81), which was exacerbated when there were few Black persons at the site (Table 3b). In PROMISE (N=523), there was evidence of a lower rate of enrollment in Hispanic persons relative to non-Hispanic White PwCF (RR=0.66 95% CI 0.56, 0.79), which also showed evidence of being strongest in sites with fewer Hispanic persons (Table 3b). In CHEC-SC (N=2,998), RR for study enrollment among Hispanic relative to non-Hispanic White persons was 0.94 (95% CI 0.89, 0.99). After stratifying on number of Hispanic persons at the

site, there was evidence of lower rate of enrollment among sites with few (i.e., 1 to 2) Hispanic persons at the site (RR=0.72, 95%CI 0.64, 0.79). There was evidence of significantly lower enrollment rate among Black PwCF in PROSPECT (RR=0.33, 95% CI 0.21, 0.53; Table 3a). This was not found in GOAL (N=216) among Black PwCF compared to the reference group however confidence intervals were wide (RR=1.22, 95% CI 0.8, 1.74). In PROSPECT (N=209), enrollment of Hispanic PwCF compared to non-Hispanic White patients was higher (RR=2.04, 95% 1.64, 2.53). In GOAL, there was no significant difference in enrollment by ethnicity (RR=1.08, 95% 0.78, 1.58).

Discussion:

We found that study enrollment rate of Black PwCF was lower than expected in two large modulator studies, the CHEC-SC and PROMISE studies. This association was stronger when there were fewer Black PwCF represented at respective registry sites. Similarly, we found that the enrollment rate for Hispanic PwCF was lower than non-Hispanic White PwCF in the PROMISE modulator study and this association was most prominent at sites with fewer Hispanic persons. In PROSPECT, there was a significantly lower enrollment rate among Black PwCF yet there was notably higher enrollment of Hispanic PwCF in the study. The direction of association was opposite in the GOAL study, with trend toward higher enrollment of both Black and Hispanic PwCF. However, the confidence intervals around the estimates of association were wide in both PROSPECT and GOAL, likely due to the relatively small sample sizes of 209 and 216 participants, respectively. The mixed findings across the four modulator studies are likely in part a reflection of study size but may also suggest that study setting and design influence inclusivity. Our sample of studies enrolled across a large period of time, with PROMISE and CHEC-SC enrolling more recently in 2019 to 2020 and 2018 to 2021, respectively. Generally findings between these two studies are consistent and we do not see a trend that earlier studies, such as GOAL (enrolling in 2012), were less inclusive.

After adjusting for potential confounders related to study participation in modulator studies, such as health status measures and socioeconomic status, we observed lower enrollment rates for Black and Hispanic individuals in the two largest studies. Prior research outside of CF has explored the barriers to representative and equitable research enrollment. In cardiology and oncology studies, restrictive eligibility criteria, homogenous study leadership, and burdensome follow up processes have been identified as barriers(22–24). Our study shows that recruitment is not necessarily representative even in studies with a lower burden of follow up like CHEC-SC where there was only one study visit for specimen collection. Prior studies in CF have found that individuals with worse health status were more likely to participate in clinical research (4). In evaluating associations of confounding variables with race and ethnicity, we found that Black and Hispanic PwCF were less likely to live further away from study centers, this finding was consistent across studies. This is important to highlight as travel and distance to study center is often referenced as a critical barrier contributing to disparities in study enrollment(24). Our findings suggest that minoritized PwCF may generally live closer to study centers and there is evidence of lower enrollment rates even after for adjusting for distance.

An important strength of our study is the ability to identify individual persons at each study site who were eligible and did not enroll. Thus we are able to construct detailed, site-level and individual-level characteristics for this non-enrolled cohort, which provides a more precise

method of accounting for confounding than using population averages. From these data we are not able to discern whether these patients were approached or not and if they declined participation or were not given the opportunity. More research is needed to explore barriers and facilitators to enrolling among these communities and understand current recruitment practices among CF TDN centers.

Our study had several limitations. These relationships are complex and socioeconomic status (SES) may act as a mediator in the association between race and outcomes. However, since both SES and race share a common origin in historical and ongoing structural racism (see Figure 1), SES also serves as a confounder in the association between reported race and study enrollment. Thus, there is no analytic approach that allow us to distinctly separate the influences of SES and race. Collapsing ethnic and racial groups with different experiences of racism into pre-set categories adds bias and imprecision. Aggregation of ethnic and racial groups may in fact mask differences in health burdens between individual cultural groups(25). Additionally, misclassification of race or ethnicity may occur based on reporting in registry or study data. Importantly, TDN sites are a subset of all CF centers, and our findings may not represent trends at all CF sites. While CFFPR data are included for most PwCF (approximately 77-85% depending on year) that there may be impactful differences in individuals not participating in the registry.(26) For example, those of older age born prior to widespread newborn screening and those of minoritized race are less likely to be diagnosed and therefore less likely to be included in the CFFPR. Similarly, the CF TDN comprises a large number of CF centers but does not include all CF centers or all healthcare settings caring for PwCF. One limitation of inverse probability weighting that it does not guarantee causal inference (27). It relies on two key assumptions: 1) all confounders must be measured and included in the model, and 2) like other regression methods, IPW can be biased if the model is misspecified, meaning for example it incorrectly assumes a linear relationship when the true relationship is more complex (e.g., quadratic).

We found evidence of lower enrollment rate among Black/ African American and Hispanic PwCF in recent CF modulator studies. Enrollment disparities were more pronounced at sites with fewer minoritized people. The association persisted despite adjusting for important clinical, demographic, and social variables including distance from study center. These findings underscore the need for more inclusive recruitment strategies to ensure diverse representation in clinical studies. Future research should explore the underlying mechanisms and study design factors contributing to these disparities as well as barriers people experience to enrollment.

Acknowledgements
The authors would like to thank the Cystic Fibrosis Foundation for the use of CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers, and clinic coordinators at CF centers throughout the United States for their contributions to the CF Foundation Patient Registry.

Tables and Figures:

Table 1. Baseline Characteristics Baseline characteristics by whether ever enrolled into any modulator study or participating in the CFFPR and eligible but not enrolled in study.

Baseline characteristics	Modulator eligible at CFFPR site but not enrolled N=14,888	Modulator study enrollee N=3594
Male	7,698 (52%)	1,821 (51%)
Race / Ethnicity		
Non-Hispanic White	12,932 (87%)	3,168 (88%)
Non-Hispanic Black	322 (2%)	51 (1%)
Other race	328 (2%)	68 (2%)
Hispanic	800 (5%)	201 (6%)
Unknown ethnicity	506 (3%)	106 (3%)
BMI category		
Underweight	885 (6%)	170 (5%)
Normal	9213 (62%)	2471 (69%)
Overweight	2849 (19%)	674 (19%)
Obese	1138 (8%)	258 (7%)
Unknown	803 (5%)	21 (1%)
Genotype		
F508 Heterozygous	7,703 (52%)	2026 (56%)
F508 Homozygous	6,202 (42%)	1307 (36%)
G551D (not F508)	174 (1%)	108 (3%)
R117H (not F508)	678 (5%)	114 (3%)
Other	131 (1%	39 (1%)
Age (median, Q1, Q3)	25 (15, 36)	19 (14, 28)
Age category		
<10	1993 (13%)	447 (12%)
10 to 19	3305 (22%)	1521 (42%)
20 to 29	3935 (26%)	863 (24%)
30 to 39	2946 (20%)	432 (12%)
40 to 49	1456 (10%)	188 (5%)
50+	1253 (8%)	143 (4%)
Insurance		
Private	8942 (60%)	2423 (67%)
Other	5378 (36%)	1141 (32%)
Unknown	568 (4%)	30 (1%)
Education		
Up to high school	2917 (18%)	533 (15%)
At least some college	5793 (39%)	1234 (34%)
Unknown	6376 (43%)	1827 (51%)
Parent Education		
Up to high school	1848 (12%)	456 (13%)
At least some college	5581 (38%)	1663 (46%)
Unknown	7459 (50%)	1475 (41%)
FEV1% predicted (median, Q1, Q3)	83 (61, 98)	89 (70, 102)
FEV1% predicted		
< 40	1142 (8%)	196 (6%)
40 to 89	5924 (40%)	1543 (43%)
90+	4746 (32%)	1648 (46%)

Unknown	3076 (21%)	207 (6%)
Exacerbation history at baseline		
None	11804 (79%)	2643 (74%)
1 to 2	2407 (16%)	764 (21%)
At least 3	677 (5%)	187 (5%)
At least 3 annual visits at baseline	7990 (54%)	2961 (82%)
CF-related diabetes at baseline		
No	10,738 (72%)	2828 (79%)
Yes	3874 (26%)	761 (21%)
Unknown	276 (2%)	5 (<1%)
Minimum distance to study site*		
< 30 miles	5369 (36%)	1849 (51%)
30 to 59 miles	2934 (20%)	704 (20%)
60 + miles	6465 (43%)	1029 (29%)
Unknown	120 (1%)	12 (<1%)

* Computed between location at centroid of home zip code to that of study participating study sites for the relevant (eligible) study.

Table 2a. Number of persons of Black race in CFFPR at sites, and frequencies found*

Number of Black persons at the site	Any	0	1	2 to 4	5+
Number of sites with that count	142	33	38	42	29
Total Black persons eligible at those sites	400	0	38	127	235
Total persons eligible at those sites	18,492	2,800	4,543	5,783	5,356
Proportion eligible who are Black	2.2%	0.0%	0.8%	2.2%	4.4%
Average site size (eligible persons)	130	85	120	138	185

*This table collapses all studies together and includes all persons enrolled in any of the four studies

Table 2b. Number of persons of Hispanic ethnicity in CFFPR at sites, and frequencies found*

Number of Hispanic persons at the site	Any	0	1 to 2	3 to 8	9+
Number of sites with that count	142	16	47	44	35
Total Hispanic persons eligible at those sites	1001	0	69	229	703
Total persons eligible at those sites	18,492	1,251	4,800	6,268	6,163
Proportion eligible who are Hispanic	5.4%	0.0%	1.4%	3.6%	11.4%
Average site size	130	78	102	142	176

*This table collapses all studies together and includes all persons enrolled in any of the four studies

Table 3a. Association of race and ethnicity with study enrollment, both unadjusted and inverse propensity (IP) weighted for known and measured confounders.

Risk ratio for enrollment	CHEC-SC	PROMISE	PROSPECT	GOAL
Black vs White				
Unadjusted	0.71 (0.51, 0.98)	0.81 (0.45, 1.46)	1.08 (0.34, 3.45)	1.18 (0.51, 2.75)
IP weighted	0.83 (0.77, 0.90)	0.68 (0.57, 0.81)	0.33 (0.21, 0.53)	1.22 (0.86, 1.74)
Hispanic vs Non-Hispanic White				
Unadjusted	0.85 (0.72, 1.00)	0.88 (0.57, 1.36)	1.93 (1.09, 3.41)	1.49 (0.77, 2.89)
IP weighted	0.94 (0.89, 0.99)	0.66 (0.56, 0.79)‡	2.04 (1.64, 2.53)	1.08 (0.73, 1.58)

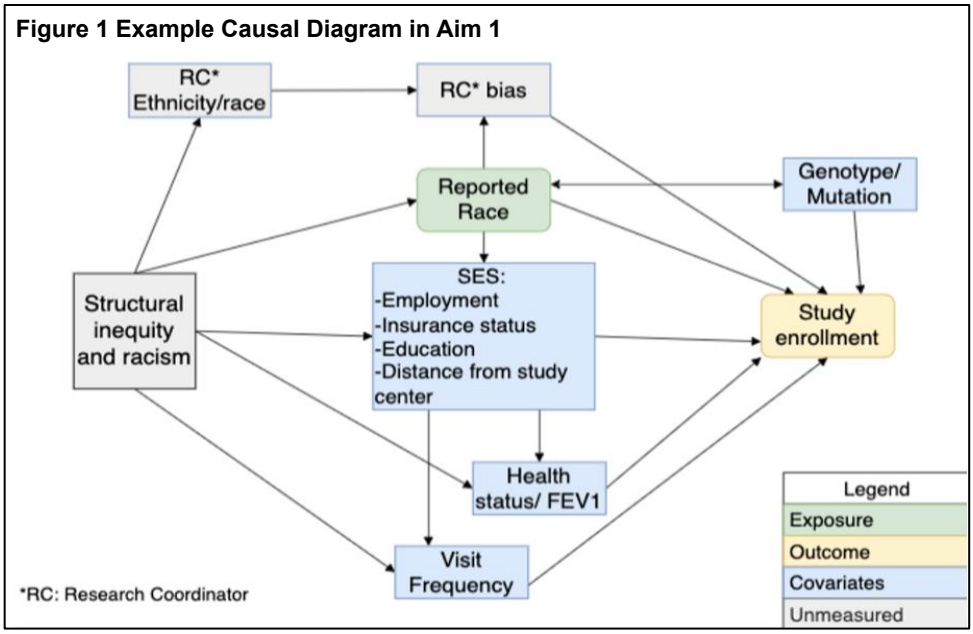
‡ For PROMISE because of convergence issues, we excluded 17 sites with only 1 eligible Hispanic person at those sites.

Table 3b. Regression results for Poisson regression stratified by numbers of person at each site of that race/ethnicity, inverse propensity (IP) weighted for known and measured confounders

IP weighted risk ratio for enrollment	CHEC-SC	PROMISE	PROSPECT	GOAL
Black vs White				
1 Black PwCF at site	0.35 (0.27, 0.45)		2.72 (1.16, 6.34)	
2 to 4 Black PwCF at site	0.72 (0.64, 0.79)*	0.54 (0.43, 0.67)ψ	0.22 (0.11, 0.44)*	1.17 (0.63, 2.17)ψ
5+ Black PwCF at site	1.28 (1.14, 1.44)*	1.00 (0.75, 1.32)*	0.11 (0.04, 0.35)*	1.21 (0.79, 1.85)
Hispanic vs Non-Hispanic				
1 to 2 Hispanic PwCF at site	0.72 (0.63, 0.81)		1.60 (0.88, 2.90)	
3 to 8 Hispanic PwCF at site	1.25 (1.14, 1.37)*	0.65 (0.53, 0.80)ψ	0.44 (0.26, 0.75)*	1.50 (0.73, 3.07)ψ
9+ Hispanic PwCF at site	0.83 (0.75, 0.91)	0.98 (0.78, 1.22)	3.41 (2.43, 4.58)*	0.93 (0.59, 1.46)

* Interaction between influence of race/ethnicity and number of Black or Hispanic PwCF at the site on enrollment was significant, $p<0.05$, relative to the reference category which is always lowest number of POC at site. ψ For two studies, there were no Black persons enrolled at sites with only 1 Black person eligible. So for convergence purposes, the rate was combined with sites where 2 to 4 Black persons were eligible. Similarly, there were no Hispanic persons enrolled at sites where only 1 to 2 Hispanic persons were eligible

Figure 1 Example Causal Diagram in Aim 1



References:

1. Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation;2022.
2. Ong T, Ramsey BW. Cystic Fibrosis: A Review. *JAMA* 2023;329:1859.
3. Dobra R, Davies G, Pike K, Strassle C, Allen L, Brendell R, *et al.* Optimising equity of access: how should we allocate slots to the most competitive trials in Cystic Fibrosis (CF)? *Journal of Cystic Fibrosis* 2021;20:978–985.
4. Goss CH, Rubenfeld GD, Ramsey BW, Aitken ML. Clinical Trial Participants Compared with Nonparticipants in Cystic Fibrosis. *Am J Respir Crit Care Med* 2006;173:98–104.
5. McGarry ME, McColley SA. Minorities are Underrepresented in Clinical Trials of Pharmaceutical Agents for Cystic Fibrosis. *Annals ATS* 2016;AnnalsATS.201603-192BC.doi:10.1513/AnnalsATS.201603-192BC.

6. Januska MN, Langfelder-Schwind E, Plachta A, Demarco T, Walker PA, Berdella MN. Center-level self-study identifies opportunities to advance equity in cystic fibrosis clinical trial participation. *Journal of Cystic Fibrosis* 2023;22:665–668.
7. Hamosh A, FitzSimmons SC, Macek M, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *The Journal of Pediatrics* 1998;132:255–259.
8. 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;149:380–389.
9. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R. Disparities in Mortality of Hispanic Patients with Cystic Fibrosis in the United States. A National and Regional Cohort Study. *Am J Respir Crit Care Med* 2018;198:1055–1063.
10. Watts KD, Seshadri R, Sullivan C, McColley SA. Increased prevalence of risk factors for morbidity and mortality in the US Hispanic CF population. *Pediatric Pulmonology* 2009;44:594–601.
11. Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, *et al.* The Cystic Fibrosis Foundation Patient Registry. Design and Methods of a National Observational Disease Registry. *Annals ATS* 2016;13:1173–1179.
12. Guimbellot JS, Baines A, Paynter A, Heltshe SL, VanDalfsen J, Jain M, *et al.* Long term clinical effectiveness of ivacaftor in people with the G551D CFTR mutation. *Journal of Cystic Fibrosis* 2021;20:213–219.
13. Shaw M, Khan U, Clancy JP, Donaldson SH, Sagel SD, Rowe SM, *et al.* Changes in LCI in F508del/F508del patients treated with lumacaftor/ivacaftor: Results from the prospect study. *Journal of Cystic Fibrosis* 2020;19:931–933.
14. Mayer-Hamblett N, Zemanick E, Odem-Davis K, VanDevanter D, Warden M, Rowe S, *et al.* Characterizing CFTR modulated sweat chloride response across the cf population: Initial

results from the CHEC-SC study. *Journal of Cystic Fibrosis* 2022;S1569199322006257.doi:10.1016/j.jcf.2022.07.008.

15. Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, *et al.* Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial. *Am J Respir Crit Care Med* 2022;205:529–539.

16. 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;56:1496–1503.

17. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8:70.

18. Textor J, Van Der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty.' *Int J Epidemiol* 2017;dyw341.doi:10.1093/ije/dyw341.

19. Symerio. pgeocode: Fast and accurate geocoding of postal codes. GitHub. Published 2020. Accessed March 17, 2025. https://github.com/symerio/pgeocode.

20. GeoNames. GeoNames. GeoNames. Published 2006. Accessed March 17, 2025. http://geonames.org/.

21. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

22. Taffe MA, Gilpin NW. Racial inequity in grant funding from the US National Institutes of Health. *Elife* 2021;10:e65697.

23. Klamerus JF, Bruinooge SS, Ye X, Klamerus ML, Damron D, Lansey D, *et al.* The impact of insurance on access to cancer clinical trials at a comprehensive cancer center. *Clin Cancer Res* 2010;16:5997–6003.

24. Clark LT, Watkins L, Piña IL, Elmer M, Akinboboye O, Gorham M, *et al.* Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Current Problems in Cardiology* 2019;44:148–172.

25. Gordon NP, Lin TY, Rau J, Lo JC. Aggregation of Asian-American subgroups masks meaningful differences in health and health risks among Asian ethnicities: an electronic health record based cohort study. *BMC Public Health* 2019;19:1551.

26. Cromwell EA, Ostrenga JS, Todd JV, Elbert A, Brown AW, Faro A, *et al.* Cystic fibrosis prevalence in the United States and participation in the Cystic Fibrosis Foundation Patient Registry in 2020. *Journal of Cystic Fibrosis* 2023;22:436–442.

27. Lederer DJ, Bell SC, Branson RD, Chalmers JD, Marshall R, Maslove DM, *et al.* Control of Confounding and Reporting of Results in Causal Inference Studies. Guidance for Authors from Editors of Respiratory, Sleep, and Critical Care Journals. *Annals ATS* 2019;16:22–28.