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Original Article

Disparities in first evaluation of infants with cystic fibrosis since implementation of newborn screening

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ABSTRACT

Objective: We evaluated whether implementation of cystic fibrosis (CF) newborn screening (NBS) leads to equitable timeliness of initial evaluation. We compared age at first event (AFE, age at sweat test, encounter and/or care episode) between infants categorized as Black/African American, American Indian/Native Alaskan, Asian, and/or Hispanic and/or other (Group 1) to White and not Hispanic infants (Group 2).

Methods: This retrospective cohort study from the Cystic Fibrosis Foundation Patient Registry (CFFPR) included infants born 2010-2018. Race and ethnicity categories followed US Census definitions. The primary outcome was AFE; the secondary outcome was weight for age (WFA) z-score averaged 12 to < 24 months. We compared distributions by Wilcoxon rank-sum test and proportions by Chi-square or Fisher's exact tests. A nested cohort study used a linear mixed effects model of variables that affect WFA, chosen *a priori*, to evaluate associations with 1-year WFA z-score.

Results: Among 6354 infants, 21% were in Group 1. Group 1 median AFE was 31 days (IQR 19, 49) and Group 2 was 22 days (IQR 14,36) ($p < .001$). Median WFA z-score at 1-2 years was lower in Group 1. In 3017 infants with complete data on variables of interest, AFE, Black race, *CFTR* variant class I-III, prematurity and public insurance were associated with lower 1-year WFA z-score.

Conclusions: Differences in AFE for infants with CF from historically marginalized groups may exacerbate long standing health disparities. We speculate that inequitable identification of *CFTR* gene variants and/or bias may influence timeliness of evaluation after an out-of-range NBS.

1. Introduction

Marked disparities in health and mortality in people with cystic fibrosis (CF) are associated with race, ethnicity, and socioeconomic status (SES) [1–12] In the US, the risk factors best defined are low SES and Hispanic ethnicity, both associated with worse lung disease and decreased survival. Low SES, but not Hispanic ethnicity, is associated with worse nutrition. Diagnosis and early therapy through newborn screening (NBS) prevents severe complications in the first months of life [13,14] and improves long term

Abbreviations: AFE, Age at first event for evaluation of CF; CF, cystic fibrosis; CFFPR, CF Foundation Patient Registry; *CFTR*, cystic fibrosis transmembrane conductance regulator; HFA, height for age; IRT, immunoreactive trypsinogen; NBS, newborn screening; SES, socioeconomic status; WFA, weight for age.

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growth [15]. With establishment of CF NBS by December 2009, equity in diagnosis was expected [14], a goal of NBS demonstrated by implementation of screening for severe combined immunodeficiency [16]. Newborn screening is generally conducted by public health department laboratories that are linked to follow-up programs. Most use a single sample, two-step algorithm. Immunoreactive trypsinogen (IRT), a pancreatic zymogen elevated in the blood of infants with CF [17,18] is measured; when elevated, DNA is extracted to test a panel of common *CFTR* variants. A test is out-of-range when elevated IRT and 1-2 pathogenic *CFTR* variants are detected. Screening results are generally sent to primary care offices, who refer infants with out-of-range tests to facilities with expertise in diagnostic testing and treatment. While rapid referral is recommended for all infants with an out-of-range test, the presence of one, instead of two, *CFTR* variants may raise less clinical concern and delay evaluation.

Most NBS laboratories use *CFTR* variant panels that detect most variants in people of northern European ancestry. While race is a social construct, *CFTR* variant distribution differs by demographic race and ethnicity. About 90% of people with CF in the US categorized as White and not Hispanic have at least one copy of the most common variant, F508del [19–21]. Those categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race groups, and/or Hispanic ethnicity less often have F508del [19,21], have different distributions of *CFTR* variants [21–23] and have more rare variants [19–21]. Concern that inequitable detection of CFTR variants would create diagnostic disparity was raised during US NBS implementation [20], and decreased *CFTR* variant detection in Hispanic infants with CF was found in Illinois [24]. In 2019, a parent contacted the Cystic Fibrosis Foundation, asking if disparities in timeliness of diagnosis might affect Black/African American babies. Also expressed was possible healthcare provider bias against a CF diagnosis in people perceived to have ancestry outside of Europe [25]. While the seminal 1938 article describing CF included Black and Hispanic children [26], medical literature often introduces CF as “the most common life-shortening genetic disease affecting Caucasians” [27], even when discussing NBS [28]. Bias could influence timeliness of referral after an out-of-range NBS test, even as racial and ethnic diversity of the US CF population increases [21]. We identified no published data on timeliness related to demographics for any genetic disorder on the NBS panel and committed to studying this issue in a planned evaluation of outcomes of CF NBS in the US.

Infants with CF had improved health during years spanning NBS implementation [29]. Timeliness goals are established for NBS programs [30], as are recommendations that infants with out-of-range NBS tests for CF have diagnostic evaluation by 28 days of age [31,32]. We previously summarized outcomes of infants with CF born during the first 9 years of universal CF NBS screening in the US [33]. Our objective for this study was to explore whether infants with CF who are demographically categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity had a later age at first testing or clinical evaluation than White and not Hispanic infants and whether this would be associated with differences in growth. We described subgroups with specific attention to the paradoxical finding that while older children and adults with CF and Hispanic ethnicity have worse lung disease, nutrition is well-preserved [3].

2. Methods

As described [3], this cohort included participants in the CFFPR born 2010-2018 with age at diagnosis and first CF Center event at 0 to 365 days. The CFFPR includes 81-84% of people with CF in the US; methods have been described [34]. Demographic race and ethnicity categories use US Census definitions. Race categories were Black/African American, White, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, two or more races, none of these or unknown. Ethnicity categories were Hispanic, not Hispanic, or unknown. Trained staff at CF Centers enter data without specific instructions for data collection, or indication of whether self-report is used for demographic data.

The primary outcome was age at first event (AFE), calculated using the earliest date of a sweat test, and/or clinical encounter, and/ or care episode lasting > 24 hours at a CF center (usually a hospitalization). More than one event could occur on the same day. This clinically meaningful measure was chosen *a priori* because the CF center-reported median age at diagnosis is lower than median AFE. The independent variable was racial and ethnic category. Group 1 included infants in categories Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity, a composite chosen based on the primary objective. Group 2 included infants described as White and not Hispanic. We described subgroups in major categories of a. Black/African American, American Indian/Native Alaskan, Asian and/or other race without Hispanic ethnicity; b. White with Hispanic ethnicity; and c. Black/African American, American Indian/Native Alaskan, Asian and/or other race with Hispanic ethnicity.

We explored a secondary outcome, weight-for-age (WFA) z-score, using World Health Organization growth charts, averaged at all visits between 12 and 24 months of age for univariable analysis. We chose this time frame due to rapid growth in the first two years of life, giving a more stable measurement than a single time point. We also compared height-for-age (HFA) z-score between 12 and 24 months, use of nutritional supplements (via oral or enteral feeding), clinic visits and hospitalizations, and rates of *Pseudomonas aeruginosa* infection.

We explored other demographic and clinical data that could influence AFE and health [6,7,35,36]. SES measures included parental educational attainment (5 categories spanning less than high school to a graduate degree), health insurance type, median income by zip code (MIZ) and household size. The MIZ was defined by US Census Bureau 2013-2017 American Community Survey 5-Year Estimates. Preterm birth and low birth weight are associated with higher rates of insufficient sweat collection for quantitative chloride testing [37] and lower WFA; we examined gestational age (full term or preterm, defined as <37 weeks GA) and birth weight percentile. Other data relevant to nutrition included *CFTR* genotype and pancreatic insufficiency. In CFFPR, *CFTR* variants are classified based on whether the defect causes absent, dysfunctional, or decreased function, as described by McKone [35,36]. Class I, II and III variants are associated with pancreatic insufficiency, class IV-V are associated with pancreatic sufficiency, and rare variants are often unclassified [21,36]. We defined pancreatic insufficiency as use of pancreatic enzyme replacement therapy (PERT) during the first year of life. There is significant missing data in CFFPR on the more accurate fecal pancreatic elastase [33,38].

Following initial analyses, we conducted a nested cohort study of a subgroup of infants to consider the impact of variables, selected *a priori* on nutritional status at one year of age. This cohort included only participants with complete data on variables of interest. To further explore these associations, we included race and ethnicity as separate variables, and included gestational age at birth, meconium ileus/ intestinal obstruction, initial sweat chloride value, genotype class, insurance, MIZ category (in tertiles), and CF center (nested in geographic region of birth) on WFA Z-score closest to the first birthday, recorded at 11-15 months.

The CFFPR is approved by local Institutional Review Boards. Written informed consent is obtained from parents or legally authorized representatives for each child’s participation.

3. Statistical analysis

Descriptive data were summarized for groups and sub-groups. Tests compared data from Group 1 to Group 2, using complete case analysis. Observations with missing data on a variable were excluded from the corresponding test. Continuous variables were compared by the Wilcoxon rank-sum test and proportions by the Chi-square or Fisher's exact test. A p-value of <.05 was considered statistically significant. Adjustments for multiple comparisons were not made, given the exploratory nature of the study and our focus on primary and secondary outcomes [39].

For the nested cohort study, a linear mixed effects model with a random program effect, nested in geographic region, assessed the impact of *a priori* defined variables on WFA z-score, accounting for clustering of patients within programs. The program effect was added to account for CF Center practice variation.

4. Results

As described previously [33], among 6879 infants born 2010-2018 and enrolled in CFFPR, 154 (2.2%) had a date of diagnosis before birth, i.e., prenatal identification, and 371 (5.4%) had AFE >365 days of age. Demographics of the remaining 6354 infants are summarized in Table 1. The distribution of race and ethnicity categories within the US Census region of birth reflected the general population. Group 1 comprised 21% of infants, who were more often insured by Medicaid, less often had private insurance, and had lower MIZ than Group 2. There were other statistically significant differences that were numerically small. Some SES variables, including parental education, had significant missing data, so while differences were seen in distributions, they may not be representative of the population. Subgroup demographics are described in major categories in Supplemental Table 1.

Diagnostic findings and AFE are summarized in Table 2. Median AFE was later and more widely distributed in Group 1: 31 (IQR 19,49) compared to 22 (IQR 14,36) days in Group 2 (p <.001). Both groups' most frequent first event was sweat testing, but Group 1 less often had an encounter (e.g., clinical evaluation) on the same day. Birth weight was missing in more than half of infants. Group 1 infants less often had a positive NBS or prenatal screening, but the difference was small. In contrast, Group 1 more often had DNA analysis reported as a diagnostic finding, suggesting identification of *CFTR* variants not reported on the NBS test. Meconium ileus incidence was not significantly different between groups. Most infants had no symptoms at diagnosis, but Group 1 had more respiratory symptoms and failure to thrive. Most infants had two *CFTR* variants reported, but distribution of *CFTR* variants was different between groups: 67% in Group 1 and 86% in Group 2 had known class I-V variants, suggesting more rare variants in Group 1. More Group 2 patients were prescribed PERT during the first year of life.

Fig. 1 shows the distribution of AFE (panel a) and average median WFA (panel b) and HFA z-scores (panel c) at 12–24-months. Nutritional outcomes are summarized in Table 3. At initial clinic visit, there was no difference in median WFA z-score, but Group 1 had lower median HFA z-score and a higher frequency of infants with HFA z-score < 10^{th} percentile. There was no difference in use of supplemental feedings. Because nutritional abnormalities are more frequent in pancreatic insufficient infants, we performed a limited post-hoc comparison of AFE and nutrition outcomes, restricted to infants prescribed PERT, summarized in Table 4. There was a similar difference in median AFE in this analysis, but Group 1 less often had AFE before 30 days of age. There was a similar difference in WFA and HFA z-scores between groups.

Healthcare utilization and infection during the first year of life are summarized in Supplemental Table 2. The median number of

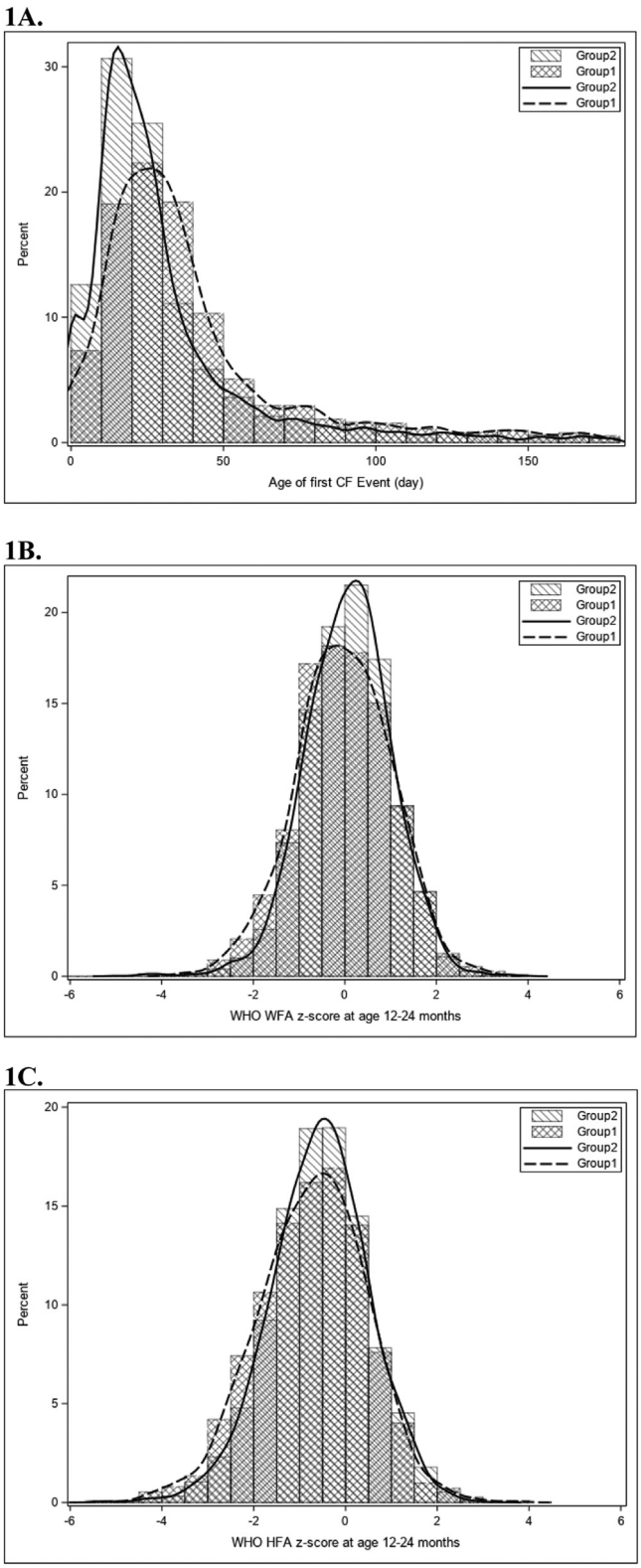

Fig. 1. Age at first CF center Event and nutritional outcomes in infants with CF born 2010-2018 demographically categorized as Black/African American, American Indian/Native Alaskan, Asian, and/or other race, and/or Hispanic (Group 1) or White and not Hispanic infants (Group 2). a. Distribution of Age at First Event b. Distribution of World Health Organization weight-for-age z-score, average between 12-24 months of age c. Distribution of World Health Organization height-for-age z-score, average between 12-24 months of age.

Table 1
Demographics of infants with CF born 2010-2018 classified by race and ethnicity (US Census 2010 Definitions).

Patient Characteristic	Group 1(N=1335)	Group 2 (N=5019)	*P* value
Gender, N (%)			
F	660 (49)	2430 (48)	
M	675 (51)	2589 (52)	
Race, N (%)			
Black/ African American	411 (31)		
White	635 (48)	5019 (100)	
Other+	289 (22)	-	
American Indian/ Alaska Native	21 (7)	-	
Asian	21 (7)	-	
Native Hawaiian/Pacific Islander	6 (84)	-	
None of the above	243 (84)	-	
Hispanic ethnicity			
No	423 (32)	4776 (95)	
Yes	842 (63)	-	
Unknown	70 (5)	243 (5)	
Health insurance, 0-365 days, N (%)			
Any Health insurance++	985 (99)	4091 (100)	.01
More than one type of insurance	119 (12)	650 (16)	.002
Private Insurance Policy	266 (27)	2235 (54)	<.001
Medicaid	640 (64)	1922 (47)	<.001
State special needs program	153 (15)	391 (10)	<.001
Other++	46 (5)	217 (5)	.40
Missing	338	997	
Household income based on zip code, US dollars			
Median, in thousands (N, IQR)	51 (40, 66)	56 (45, 72)	<.001
Lowest median income quartile in cohort	409 (34)	1047 (23)	<.001
Missing	126	377	
US Census Region of Birth			
Northeast	163 (12)	612 (12)	<.001
Midwest	185 (14)	1281 (26)	
South	380 (29)	1461 (29)	
West	289 (22)	689 (14)	
Unknown/Foreign	318 (24)	976 (20)	
Father's education (first year infant enrolled)			<.001
Less than High School	87 (18)	156 (7)	
High School diploma or equivalent	202 (42)	722 (30)	
Some College	98 (21)	513 (21)	
College Graduate	66 (14)	789 (33)	
Masters/Doctoral level degree	24 (5)	222 (9)	
Missing	858	2617	
Mother's education (first year infant enrolled)			<.001
Less than High School	98 (185)	153 (6)	
High School diploma or equivalent	195 (37)	668 (27)	
Some College	130 (25)	546 (22)	
College Graduate	78 (25)	923 (37)	
Masters/Doctoral degree	28 (5)	228 (9)	
Missing	806	2403	
Number of people in household (participant included, first year in registry)			<.001
2	28 (3)	53 (2)	
3	259 (30)	1346 (37)	
4	258 (30)	1212 (33)	
5	167 (19)	621 (17)	
6	72 (8)	234 (6)	
7	39 (5)	93 (3)	
8 or more	40 (5)	72 (2)	
Missing	472	1388	

Group 1: infants categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity. Group 2: infants categorized as White and not Hispanic. +other race categories can include one or more other race. ++ health insurance categories are not mutually exclusive. +++ includes military health plans, Medicare, Indian Health Service, and others.

CF Center visits was 8 for Group 1 and 9 for Group 2. The rate of hospitalizations for pulmonary exacerbation was higher in Group 1, but the rate of *Pseudomonas aeruginosa* infection was not.

Fig. 2 shows the consort diagram for 3017 infants with complete data for *a priori* defined variables included in the nested cohort study. The linear mixed effects model in Table 5 demonstrates that AFE, prematurity, Black race, class I-III variants, and public insurance were associated with lower WFA z-score at 1 year of age. Higher MIZ, compared to median MIZ, was associated with higher WFA z-score.

5. Discussion

This exploratory investigation demonstrates that infants demographically categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity, are older at AFE and have poorer early nutritional outcomes than those categorized as White and not Hispanic. We found that lower WFA z-score at one year was associated with later AFE, Black/African American race, and public insurance. The descriptive nature of this study, significant missing data for some variables,

Table 2
Diagnostic and Clinical Findings in infants with CF born 2010-2018 classified by race and Hispanic ethnicity (US Census 2010 Definitions).

Patient Characteristic	Group 1(N=1335)	Group 2(N=5019)	*P* value
Age at diagnosis, days, median (IQR)	21 (7, 42)	13 (3, 26)	<.001
Age at first CF event, days, median (IQR)	31 (19, 49)	22 (14, 36)	<.001
First CF Event			
Sweat Test N (%)	927 (69)	3117 (62)	<.001
Encounter N (%)	577 (43)	2650 (53)	<.001
Care episode > 24 hours N (%)	100 (8)	407 (8)	0.46
CFTR Variant Class N (%)			
Class I-III	709 (53)	3598 (72)	<.001
Class IV, V	185 (14)	701 (14)	
Other Variant class, both alleles known	388 (29)	585 (12)	
One allele missing or unknown	37 (3)	52 (1)	
Both alleles missing or unknown	16 (1)	83 (2)	
Sweat testing			
Age at first sweat test median (IQR)	36 (24, 70)	28 (18, 55)	< .001
Missing N (%)	99 (7)	486 (9)	
Initial sweat test QNS++ N (%)	75 (6)	242 (5)	0.30
Missing N (%)	109 (8)	504 (10)	
Sweat test value			
Initial sweat chloride, mmol/L, median (IQR)	92 (73, 101)	95 (84, 103)	< .001
Missing N (%)	184 (14)	745 (15)	
PERT during first year of life			<.001
Taking PERT N (%)	975 (82)	4156 (87)	
Missing	145	266	
WHO birth weight z-score (≥37 GA Weeks)			
z-score category			0.002
<10th percentile	95 (17)	271 (12)	
>=10th - <25th percentile	113 (21)	406 (18)	
>=25th - <50th percentile	134 (24)	542 (24)	
>=50th percentile	209 (38)	1007 (45)	
Median (IQR)	-0.30 (-0.99, 0.51)	-0.07 (0.75, 0.57)	<.001
Missing	784	2793	
Signs and symptoms at diagnosis			
Meconium Ileus N (%)	161 (15)	692 (14)	0.10
Positive NBS N (%)	1063 (80)	4154 (83)	0.008
Prenatal screening N (%)	25 (2)	191 (4)	<.001
DNA analysis N (%)	315 (24)	977 (20)	<.001
Respiratory N (%)	61 (5)	126 (3)	<.001
Failure to thrive/ malnutrition	117 (9)	238 (5)	<.001
Steatorrhea/ loose stools N (%)	56 (4)	179 (4)	0.28

Group 1: infants categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity. Group 2: infants categorized as White and not Hispanic. [b] ++QNS responses are yes or no. [c] 0.8% of Group1 infants and 0.3% of Group 2 infants had neither answer recorded. Abbreviations: IQR, interquartile ratio; QNS, quantity not sufficient PERT, pancreatic enzyme replacement therapy.

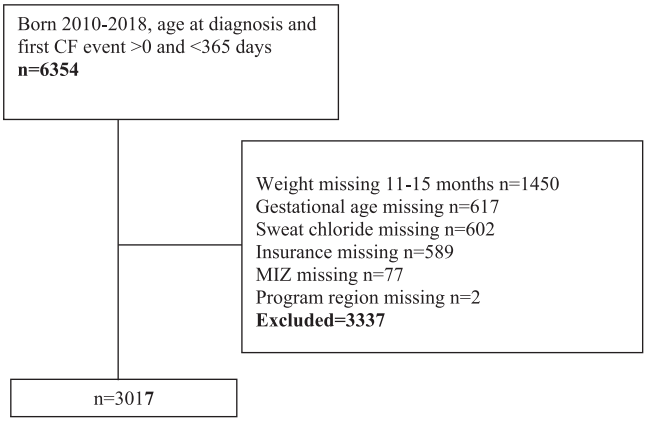

Fig. 2. Consort diagram showing disposition of cohort participants for inclusion in the multiple mixed linear effects model.

and the plethora of influences on early life health in CF allow only hypothesis generation regarding the association between AFE and early life nutritional outcomes. Prospective studies that assess barriers to prompt evaluation and implementation of CF care to demographically representative infants should be undertaken. Enhancing collection of sociodemographic data, including reduction of missing variables and self-report of race and ethnicity (where allowed) may lead to targeted interventions in countries or regions with established registries. The experience of people from minoritized groups, whose children were diagnosed with CF after implementation of newborn screening, is critically important to consider through engagement efforts and qualitative studies.

These findings may be clinically important. Early life nutritional deficits in CF [13] are associated with increased respiratory signs and symptoms [40], lower pulmonary function [41–43] and childhood mortality [9,44]. The clinical significance of a median difference 8-9 days between groups cannot be assessed using retrospective data. Variation in onset of severe pancreatic insufficiency after birth in CF [45], the influence of genetic modifiers of CF nutrition [46], and the influence of social and environmental factors [1,11] contribute to early life nutrition in CF. We previously noted that 40% of all infants in this cohort had WFA < 10th percentile at their first clinical encounter [33], while this analysis shows that > 40% of pancreatic insufficient infants have AFE ≥ 30 days.

Group 1 infants had more pulmonary exacerbations, which drive pulmonary function decline [47,48]. A prospective study of growth in infants with CF diagnosed via NBS showed no association between low weight and hospitalization [49], though race and ethnicity of participating infants was not reported in the cohort

Table 3
Nutritional Outcomes of infants with CF born 2010-2018 classified by race and ethnicity (US Census 2010 definitions).

	Group 1(N=1335)	Group 2(N=5019)	*P* value
Nutritional status at first clinic visit, N (%) reported			
WFA z-score category			0.197
<10th percentile N (%)	362 (41)	1333 (38)	
>10th - <25th percentile N (%)	158 (18)	718 (21)	
>25th - <50th percentile N (%)	174 (20)	741 (21)	
>50th percentile N (%)	179 (21)	702 (20)	
WFA z-score median (IQR)	-1 (-1.81, -0.19)	-0.92 (-1.72, -0.17)	0.175
missing	462	1525	
HFA z-score category	**N=873 (65)**	**N=3491 (70)**	0.004
<10th percentile N (%)	319 (37)	1132 (32)	
>10th - <25th percentile N (%)	175 (20)	615 (18)	
>25th - <50th percentile N (%)	176 (20)	750 (22)	
>50th percentile N (%)	203 (23)	994 (28)	
HFA z-score Median (IQR)	-0.89 (-1.76, -0.07)	-0.68 (-1.55, 0.12)	<.001
missing	462	1525	
Supplemental feeding first year N (%) reported[b]	**N=1175 (88)**	**N=4715 (94)**	
Oral supplements N (%)	476 (41)	1873 (40)	0.69
Enteral tube supplements N (%)	82 (7)	357 (8)	0.49
missing	160	304	
Nutritional status, 12 to <24 months N (%) reported			
WFA z-score, median (IQR)	-0.02 (-0.72, 0.69)	0.11 (-0.53, 0.68)	< 0.001
missing	217	663	
HFA z-score, median (IQR)	-0.66 (-1.50, 0.08)	-0.54 (-1.25, 0.14)	< 0.001
missing	217	672	

Group 1: infants categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity to Group 2: infants categorized as White and not Hispanic. [b]Reported as yes/no. Abbreviations: WFA, weight for age by World Health Organization growth charts; HFA, height for age by World Health Organization growth charts.

Table 4
First event and nutritional outcomes in pancreatic insufficient infants with CF born 2010-2018 classified by race and Hispanic ethnicity (US Census 2010 Definitions).

	Group 1 N=975	Group 2 N=4156	*P* value
Age at first CF event, days, median (IQR)	29 (17,45)	21 (13,33)	<.001
Age at first event, category, N (%)			
< 30 days	509 (52)	2928 (70)	< .001
30-59 days	298 (31)	755 (18)	
≥ 60 days	168 (17)	473 (11)	
First CF Event			
Sweat Test N (%)	611 (63)	2387 (57)	.003
Encounter N (%)	483 (50)	2386 (57)	< .001
Care episode > 24 hours N (%)	98 (10)	401 (10)	0.70
Nutritional outcomes			
Weight-for-Age, average at 12-24 months			
WHO WFA z-score Median (IQR)	-0.11 (-0.75,0.59)	0.062 (-0.57,0.65)	< .001
Missing	100	440	
Height-for-Age, average at 12-24 months			
WHO HFA z-score Median (IQR)	-0.79 (-1.59,0)	-0.59 (-1.29, 0.78)	< .001
Missing	100	446	

Group 1: infants categorized as Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity. Group 2: infants categorized as White and not Hispanic.

[50]. Group 1 infants more frequently had symptoms at presentation. The larger proportion of Group 1 infants with AFE > 30 days suggests risk for early, severe complications of CF, including hyponatremic dehydration [51] and bleeding from vitamin K deficiency [52], both sometimes fatal in the first weeks of life. Thus, inequalities in timely evaluation may worsen sociodemographic health disparities in CF.

Group 1 less often had a clinical encounter as part of the first CF event and more often had DNA analysis, suggesting that < 2 *CFTR* variants were detected by NBS. *CFTR* panels for NBS vary by state and have changed over time. Since CFFPR does not distinguish whether variants are detected by NBS or other tests, this requires further study. Some states perform *CFTR* sequencing, but only after one variant is detected on a panel [53,54]. Next generation sequencing improves detection of *CFTR* variants [55], reduces risk of false negative tests, and can be performed in one step, but is not widely used. Since extended gene sequencing detects *CFTR* variants of unknown clinical significance, an increase in cystic fibrosis screen positive, inconclusive diagnosis (*CFTR*-related metabolic syndrome in the United States) infants is expected with this approach [56]. Strategies to reduce burdens on families and health care systems, and ongoing efforts to characterize pathogenicity of

Table 5
Linear mixed effects model showing associations between a priori selected variables and WFA z-score at one year.

Variables	Estimate	Standard Error	*P*-Value
Age at First Event (AFE)	-0.004	0.001	<.0001
Gestation > =37 weeks	Reference		
Gestation <37 weeks	-0.568	0.063	<.0001
Gestation Unknown	-0.033	0.079	0.682
White Infants	Reference		
Black Infants	-0.240	0.077	0.002
Other	-0.075	0.098	0.444
Not Hispanic	Reference		
Hispanic	0.011	0.061	0.859
Unknown ethnicity	-0.01747	0.09017	0.846
Class I-III Genotype	Reference		
Class IV-V Genotype	0.200	0.067	0.003
Other Genotype	0.187	0.051	<0.001
Middle MIZ Category	Reference		
Lowest MIZ Category	0.024	0.045	0.596
Highest MIZ Category	0.163	0.045	<0.001
Private Insurance	Reference		
No Insurance	-0.195	0.257	0.448
Public Insurance	-0.078	0.039	0.047

rare variants, are required. With any algorithm, all infants with out-of-range CF NBS should be evaluated promptly, regardless race, ethnicity, or whether 1 or 2 variants is reported. Increased coordination of follow-up of out-of-range NBS results between primary care providers, CF Centers, and state NBS programs help to achieve this goal.

Given the well-known influence of low SES on health outcomes and mortality in CF and in the general population, it may be especially important to reduce barriers to timely visits at CF Centers arising from geographic and structural barriers to access. We found that Group 1 had lower SES based on several measures. The association between Medicaid insurance and poorer nutrition outcomes should be interpreted in the context of the Medicaid program's role of insuring children with lower SES; Medicaid has unequivocally reduced infant mortality for disorders detected by NBS [57]. Other factors associated with low SES are likely to contribute to worse health outcomes. A study from the United Kingdom showed that NBS does not provide clinical benefits to infants of lower SES [58], but did not report data on timeliness of evaluation. Furthermore, countries with universal health care provision show persistence of adverse health outcomes associated with low SES [59,60]. Nevertheless, reducing effects of race and ethnicity-related bias in NBS detection of CFTR variants and increasing health care professional knowledge that CF occurs in all populations can reduce compounding health effects of racism [61,62].

Limitations of this study include that racial and ethnic categories were limited to US Census definitions and were not systematically self-reported. Use of composite comparison groups [6]was a pragmatic decision, based on prior literature and the small numbers in some groups, that does not fully reflect the great diversity of the CF population. Interpretation of the mixed model assumes that those with complete data are representative of registry participants overall. The cohort was enrolled before approval of any *CFTR* modulator for infants < 1 year of age, and increased disparities in CF outcomes are expected based on reduced eligibility for these disease-modifying therapies in people with CF who are categorized as Black/African American, American Indian/Native Alaskan, Asian, and/or Hispanic [23].

Further analyses of the relationship between AFE and nutritional outcomes, and of processes that can influence timeliness of referral, are needed. Because pre-symptomatic treatment is the overarching goal of NBS, we advocate for quality improvement activities that improve timeliness of CF diagnosis for all infants, with a focus on equity in diagnostic evaluation and initiation of care.

6. Conclusion

We identified disparities in first CF Center evaluation and clinical outcomes in infants demographically categorized as Black/African American, American Indian/Native Alaskan, Asian, and/or Hispanic compared to those categorized as White and not Hispanic. Timely evaluation and care for all infants with an out-of-range CF NBS is essential for health equity in CF, and further research is needed to better understand these findings and identify interventions. Evaluation of timeliness of care after out-of-range NBS tests for other disorders is also needed to assess whether these findings are unique to CF or occur more broadly. Quality improvement efforts to assure pre-symptomatic diagnosis and treatment should not be delayed.

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Contributors' statement

Susanna A. McColley, MD, contributed to conceptualization/design, methodology, investigation, funding acquisition, and resources; drafted the initial manuscript; and edited the manuscript in preparation for submission.

Stacey L. Martiniano, MD, contributed to conceptualization/design, methodology, investigation, and reviewing and editing the manuscript.

Clement L. Ren, MD, MBA, contributed to conceptualization/design, methodology, investigation, and reviewing and editing the manuscript.

Marci K. Sontag, PhD, contributed to conceptualization/design, methodology, investigation, and reviewing and editing the manuscript.

Karen Rychlik, MS, contributed to conceptualization/design, methodology, investigation, formal analysis, and reviewing and editing the manuscript.

Lauren Balmert, PhD, contributed to conceptualization/design, methodology, investigation, formal analysis, and reviewing and editing the manuscript.

Alexander Elbert, PhD, contributed to conceptualization/design, methodology, investigation, data curation, formal analysis, and reviewing and editing the manuscript.

Runyu Wu, MS, contributed to conceptualization/design, methodology, investigation, data curation, formal analysis, and reviewing and editing the manuscript.

Philip M. Farrell, MD, PhD, contributed to conceptualization/design, methodology, investigation, and reviewing and editing the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Definitions

Event: Sweat test, care episodes, or encounter.

Date of diagnosis: CFFPR reported date of diagnosis reported by CF Center.

Care episode: An event with start and end dates that are not the same (e.g., a hospitalization).

Encounter: An event that starts and end on the same date (e.g., an ambulatory visit).

Group 1: infants demographically categorized as being from Black/African American, American Indian/ Native Alaskan, Asian, and/or other race, and/or Hispanic ethnicity.

Group 2: infants demographically categorized as White and not Hispanic.

Article summary

Infants from historically marginalized groups, categorized using US Census race and ethnicity definitions, were older at first evaluation for cystic fibrosis.

What's known on the subject

Early CF diagnosis improves long-term health, but variability in timeliness of evaluation could reduce benefits of newborn screening (NBS). There may be bias in CF diagnosis based on race or ethnicity.

What this study adds

Infants with CF categorized Black/African American, White, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, two or more races, none of these or unknown and/or of Hispanic ethnicity were older at initial CF Center evaluation than White, non-Hispanic infants.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose. Dr. Albert and Mr. Wu are employees of the Cystic Fibrosis Foundation.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2022.07.010.

References

[1] McGarry ME, Williams WA, McColley SA. The demographics of adverse outcomes in cystic fibrosis. Pediatr Pulmonol 2019;54(suppl 3):S74–83. doi:10.1002/ppul.24434.
[2] McGarry ME, Neuhaus JM, Nielson DW, Burchard E, Ly NP. Pulmonary function disparities exist and persist in Hispanic patients with cystic fibrosis: a longitudinal analysis. Pediatr Pulmonol 2017;52(12):1550–7. doi:10.1002/ppul.23884.
[3] 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. doi:10.1002/ppul.21037.
[4] 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(8):1055–63. doi:10.1164/rccm.201711-2357OC.
[5] 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. Pediatr Pulmonol 2019;54(9):1382–90. doi:10.1002/ppul.24377.
[6] O'Connor GT, Quinton HB, Kahn R, et al. Case-mix adjustment for evaluation of mortality in cystic fibrosis. Pediatr Pulmonol 2002;33(2):99–105. doi:10.1002/ppul.10042.
[7] O'Connor GT, Quinton HB, Kneeland T, et al. Median household income and mortality rate in cystic fibrosis. Pediatrics 2003;111(4 Pt 1):e333–9. doi:10.1542/peds.111.4.e333.
[8] 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. J Pediatr 1998;132(2):255–9. doi:10.1016/s0022-3476(98)70441-x.
[9] McColley SA, Schechter MS, Morgan WJ, Pasta DJ, Craib ML, Konstan MW. Risk factors for mortality before age 18 years in cystic fibrosis. Pediatr Pulmonol 2017;52(7):909–15. doi:10.1002/ppul.23715.
[10] Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. Am J Respir Crit Care Med 2001;163(6):1331–7. doi:10.1164/ajrccm.163.6.9912100.
[11] Oates GR, Schechter MS. Socioeconomic status and health outcomes: cystic fibrosis as a model. Expert Rev Respir Med 2016;10(9):967–77. doi:10.1080/17476348.2016.1196140.
[12] Britton LJ, Oates GR, Oster RA, et al. Risk stratification model to detect early pulmonary disease in infants with cystic fibrosis diagnosed by newborn screening. Pediatr Pulmonol 2016;51(11):1168–76. doi:10.1002/ppul.23536.
[13] Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics 2001;107(1):1–13. doi:10.1542/peds.107.1.1.
[14] Grosse SD, Boyle CA, Botkin JR, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. MMWR Recomm Rep 2004;53(RR-13):1–36.
[15] Campbell PW, White TB. Newborn screening for cystic fibrosis: an opportunity to improve care and outcomes. J Pediatr 2005;147(3 suppl):S2–5. doi:10.1016/j.jpeds.2005.08.016.
[16] Brosco JP, Grosse SD, Ross LF. Universal state newborn screening programs can reduce health disparities. JAMA Pediatr 2015;169(1):7–8. doi:10.1001/jamapediatrics.2014.2465.
[17] Sontag MK, Hammond KB, Zielenski J, Wagener JS, Accurso FJ. Two-tiered immunoreactive trypsinogen-based newborn screening for cystic fibrosis in Colorado: screening efficacy and diagnostic outcomes. J Pediatr 2005;147(3 Suppl):S83–8. doi:10.1016/j.jpeds.2005.08.005.
[18] Castellani C, Massie J, Sontag M, Southern KW. Newborn screening for cystic fibrosis. Lancet Respir Med 2016;4(8):653–61. doi:10.1016/S2213-2600(16)00053-9.
[19] Sugarman EA, Rohlfs EM, Silverman LM, Allitto BA. CFTR mutation distribution among U.S. Hispanic and African American individuals: evaluation in cystic fibrosis patient and carrier screening populations. Genet Med 2004;6(5):392–9 Sep-Oct 2004. doi:10.1097/01.gim.0000139503.22088.66.
[20] Ross LF. Newborn screening for cystic fibrosis: a lesson in public health disparities. J Pediatr 2008;153(3):308–13. doi:10.1016/j.jpeds.2008.04.061.
[21] Cystic Fibrosis Foundation Patient Registry 2020 Annual Data REport. Bethesda, MD; 2021.
[22] Baker MW, Groose M, Hoffman G, Rock M, Levy H, Farrell PM. Optimal DNA tier for the IRT/DNA algorithm determined by CFTR mutation results over 14 years of newborn screening. J Cyst Fibros 2011;10(4):278–81. doi:10.1016/j.jcf.2011.02.001.
[23] McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. Pediatr Pulmonol 2021. doi:10.1002/ppul.25285.
[24] 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. J Genet Couns 2012;21(5):671–5. doi:10.1007/s10897-012-9481-2.
[25] Rubin R. Tackling the misconception that cystic fibrosis is a "white people's disease". JAMA 2021. doi:10.1001/jama.2021.5086.
[26] DH A. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathological study. Am J Dis Child 1938;56:344–99.
[27] Cheng PC, Alexiou S, Rubenstein RC. Safety and efficacy of treatment with lumacaftor in combination with ivacaftor in younger patients with cystic fibrosis. Expert Rev Respir Med 2019;13(5):417–23. doi:10.1080/17476348.2019.1602040.
[28] Coverstone AM, Ferkol TW. Early diagnosis and intervention in cystic fibrosis: imagining the unimaginable. Front Pediatr 2020;8:608821. doi:10.3389/fped.2020.608821.
[29] Hoch H, Sontag MK, Scarbro S, et al. Clinical outcomes in U.S. infants with cystic fibrosis from 2001 to 2012. Pediatr Pulmonol 2018;53(11):1492–7. doi:10.1002/ppul.24165.
[30] Sontag MK, Miller JI, McKasson S, et al. Newborn screening timeliness quality improvement initiative: impact of national recommendations and data repository. PLoS One 2020;15(4):e0231050. doi:10.1371/journal.pone.0231050.
[31] Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. J Pediatr 2017;181S:S4–S15 e1. doi:10.1016/j.jpeds.2016.09.064.
[32] Farrell PM, White TB, Howenstine MS, et al. Diagnosis of cystic fibrosis in screened populations. J Pediatr 2017;181S:S33–44 e2. doi:10.1016/j.jpeds.2016.09.065.
[33] Martiniano SL, Elbert AA, Farrell PM, et al. Outcomes of infants born during the first 9 years of CF newborn screening in the United States: a retrospective Cystic Fibrosis Foundation Patient Registry cohort study. Pediatr Pulmonol 2021 Sep 01. doi:10.1002/ppul.25658.
[34] Knapp EA, Fink AK, Goss CH, et al. The cystic fibrosis foundation patient registry. Design and methods of a national observational disease registry. Ann Am Thorac Soc 2016;13(7):1173–9. doi:10.1513/AnnalsATS.201511-781OC.
[35] McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype and mortality in cystic fibrosis: a retrospective cohort study. Lancet 2003;361(9370):1671–6. doi:10.1016/S0140-6736(03)13368-5.
[36] McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. Chest. 2006;130(5):1441–7. doi:10.1378/chest.130.5.1441.
[37] McColley SA, Elbert A, Wu R, Ren CL, Sontag MK, LeGrys VA. Quantity not sufficient rates and delays in sweat testing in US infants with cystic fibrosis. Pediatr Pulmonol 2020. doi:10.1002/ppul.25027.

[38] Borowitz D, Baker SS, Duffy L, et al. Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis. J Pediatr 2004;145(3):322–6. doi:10.1016/j.jpeds.2004.04.049.
[39] Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Med Res Methodol 2002;2:8 Jun 17. doi:10.1186/1471-2288-2-8.
[40] McColley SA, Ren CL, Schechter MS, et al. Risk factors for onset of persistent respiratory symptoms in children with cystic fibrosis. Pediatr Pulmonol 2012;47(10):966–72. doi:10.1002/ppul.22519.
[41] Konstan MW, Butler SM, Wohl ME, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. J Pediatr 2003;142(6):624–30. doi:10.1067/mpd.2003.152.
[42] Sanders DB, Zhang Z, Farrell PM, Lai HJ, Group WCNS. Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis. J Cyst Fibros 2018;17(4):528–35. doi:10.1016/j.jcf.2018.01.006.
[43] Sanders DB, Slaven JE, Maguiness K, Chmiel JF, Ren CL. Early life height attainment in cystic fibrosis is associated with pulmonary function at age 6 years. Ann Am Thorac Soc; 2021. doi:101513/AnnalsATS202008-933OC.
[44] Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr 2013;162(3):530–5 e1. doi:10.1016/j.jpeds.2012.08.040.
[45] Walkowiak J, Sands D, Nowakowska A, et al. Early decline of pancreatic function in cystic fibrosis patients with class 1 or 2 CFTR mutations. J Pediatr Gastroenterol Nutr 2005;40(2):199–201. doi:10.1097/00005176-200502000-00022.
[46] Bradley GM, Blackman SM, Watson CP, Doshi VK, Cutting GR. Genetic modifiers of nutritional status in cystic fibrosis. Am J Clin Nutr 2012;96(6):1299–308. doi:10.3945/ajcn.112.043406.
[47] Sanders DB, Li Z, Laxova A, et al. Risk factors for the progression of cystic fibrosis lung disease throughout childhood. Ann Am Thorac Soc 2014;11(1):63–72. doi:10.1513/AnnalsATS.201309-303OC.
[48] Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J 2012;40(1):61–6. doi:10.1183/09031936.00159111.
[49] Goetz D, Kopp BT, Salvator A, et al. Pulmonary findings in infants with cystic fibrosis during the first year of life: results from the Baby Observational and Nutrition Study (BONUS) cohort study. Pediatr Pulmonol 2019;54(5):581–6. doi:10.1002/ppul.24261.
[50] Leung DH, Heltshe SL, Borowitz D, et al. Effects of diagnosis by newborn screening for cystic fibrosis on weight and length in the first year of life. JAMA Pediatr 2017;171(6):546–54. doi:10.1001/jamapediatrics.2017.0206.
[51] Guimarães EV, Schettino GC, Camargos PA, Penna FJ. Prevalence of hyponatremia at diagnosis and factors associated with the longitudinal variation in serum sodium levels in infants with cystic fibrosis. J Pediatr 2012;161(2):285–9. doi:10.1016/j.jpeds.2012.01.052.
[52] Hamid B, Khan A. Cerebral hemorrhage as the initial manifestation of cystic fibrosis. J Child Neurol 2007;22(1):114–15. doi:10.1177/0883073807299957.
[53] Kharrazi M, Yang J, Bishop T, et al. Newborn screening for cystic fibrosis in California. Pediatrics 2015;136(6):1062–72. doi:10.1542/peds.2015-0811.
[54] Kharrazi M. Evaluation of a new newborn screening model for cystic fibrosis. J Pediatr 2016;175:7–9. doi:10.1016/j.jpeds.2016.05.022.
[55] Baker MW, Atkins AE, Cordovado SK, Hendrix M, Earley MC, Farrell PM. Improving newborn screening for cystic fibrosis using next-generation sequencing technology: a technical feasibility study. Genet Med 2016;18(3):231–8. doi:10.1038/gim.2014.209.
[56] Bergougnoux A, Lopez M, Girodon E. The role of extended CFTR gene sequencing in newborn screening for cystic fibrosis. Int J Neonatal Screen 2020;6:23. doi:10.3390/ijns6010023.57.
[57] Sohn H, Timmermans S. Inequities in newborn screening: Race and the role of medicaid. SSM Popul Health 2019;9:100496. doi:10.1016/j.ssmph.2019.100496.
[58] Schlüter DK, Southern KW, Dryden C, Diggle P, Taylor-Robinson D. Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: a UK CF registry-based study. Thorax 2020;75(2):123–31. doi:10.1136/thoraxjnl-2019-213179.
[59] Taylor-Robinson DC, Smyth RL, Diggle PJ, Whitehead M. The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study. Lancet Respir Med 2013;1(2):121–8. doi:10.1016/S2213-2600(13)70002-X.
[60] Taylor-Robinson DC, Thielen K, Pressler T, et al. Low socioeconomic status is associated with worse lung function in the Danish cystic fibrosis population. Eur Respir J 2014;44(5):1363–6. doi:10.1183/09031936.00063714.
[61] Paradies Y, Ben J, Denson N, et al. Racism as a Determinant of health: a systematic review and meta-analysis. PLoS One 2015;10(9):e0138511. doi:10.1371/journal.pone.0138511.
[62] Heard-Garris NJ, Cale M, Camaj L, Hamati MC, Dominguez TP. Transmitting trauma: a systematic review of vicarious racism and child health. Soc Sci Med 2018;199:230–40. doi:10.1016/j.socscimed.2017.04.018.