10 days (interquartile range 8–12) in the early cohort and 47d (interquartile range 37–72) in the late cohort ($p < .001$). Late infants were more likely to have only one CFTR variant detected on commercial 23-variant panels (28%, vs 22% for early, $p = 0.01$) and 39-variant panels (26%, vs 17% for early, $p < 0.001$). Late infants were also more likely to have a sweat test as a first CF event (70%, vs 50% for early, $p < 0.001$) and less likely to have a clinical encounter as a first CF event (49%, vs 61% for early, $p < 0.001$). Breastfeeding rates were significantly lower at 2 and 6 months of age in the late infants. Late infants were less likely to have parents with reported college or graduate school education. Despite no differences in birth weight or length, late infants had lower median weight-for-age and height-for-age Z-scores at first encounter and 1 year. At 3 and 5 years, weight-for-age Z-scores were similar, but late infants had persistently lower height-for-age. There were no differences in *Pseudomonas aeruginosa* infection, pulmonary function at age 7, or hospitalization rates between cohorts.

Conclusions: Use of limited CFTR variant panels may result in later evaluation at a CF center. Although groups were matched for income, parent education may also contribute to later diagnosis, potentially because of difficulties navigating the health care system and confirmatory testing. Late diagnosis was associated with less likelihood of breastfeeding, lower weight and height at presentation and 1 year, and lower height through 5 years of age. This study highlights ongoing delays in timely NBS in the United States, with resultant long-term consequences. Qualitative studies and improvement work that evaluate more specific system factors in NBS follow-up programs are essential to ensure equitable, timely evaluation at CF care centers for all infants (MCCOLL19QI10).

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Outcomes of children with cystic fibrosis transmembrane conductance regulator–related metabolic syndrome

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Background: Newborn screening (NBS) evaluation for high immunoreactive trypsinogen level (IRT) associated with a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) mutation (IRT+/DNA+) has led to early identification and treatment of children with severe CF, although it has also identified children with genetic and biochemical findings indicating risk of CF but without symptoms or conclusive diagnostic results (CFTR-related metabolic syndrome (CRMS)). Some of these children transition to CF, but the effect of early diagnosis and treatment is unclear. This study evaluated outcomes of children designated with CRMS after NBS referral.

Methods: Children with IRT+/DNA+ on NBS referred to our CF Center from 2008 to 2020 had their charts reviewed and data collected for results of IRT, genotype, sweat chloride test (SCT) values, stool elastase, and sputum swab cultures. Children were categorized according to the most recent Cystic Fibrosis Foundation diagnostic guidelines as CFTR mutation carrier, CF, or CRMS. CRMS group was further subcategorized according to the child's final diagnosis in 2020 as CRMS transitioned to CF (CRMS-CF), CRMS transitioned to carrier (CRMS-carrier), or CRMS persistent (CRMS-P).

Results: Of 1,346 children referred for IRT+/DNA+ with a SCT, 86% were initially designated as carriers, 10% as CF, and 5% as CRMS. Mean first SCT was significantly higher for CRMS than for carriers ($p < 0.001$). Of those initially designated as CRMS (n = 63), 17.5% transitioned to CF because repeat SCT reaching diagnostic threshold, clinical symptoms, expanded genetics, or re-classification of their CFTR mutation. Of CRMS-CF, 36% had initial SCT between 30 mEq/L and 39 mEq/L, 36% between 40 mEq/L and 49 mEq/L, and 27% between 50 mEq/L and 59 mEq/L. Age of transition for this group ranged from 2.2 months to 8.4 years. Mean first SCT value was significantly higher for CRMS-CF (45 mEq/L) than CRMS-P (30.27 mEq/L) ($p < 0.001$) and CRMS-carrier (35 mEq/L) ($p = 0.003$). CRMS-CF had significantly higher values at all repeat SCTs than CRMS-P ($p < 0.001$). No association between IRT and first SCT or difference in stool elastase levels was noted for CRMS subgroups. CRMS-CF cultured more bacterial species than CRMS-carrier ($p < 0.001$) or CRMS-P ($p = 0.01$). Of children with CRMS that cultured *Pseudomonas aeruginosa,* 50% transitioned to CRMS-CF. *Pseudomonas* was cultured at least once in 19% of CRMS-CF, 7.7% of CRMS-P, and 0% of CRMS-carrier.

Conclusions: Expanded genetics and repeat SCT were helpful in diagnosing children at our CF center initially designated as CRMS who eventually transitioned to CF. Thirty-six percent of the CRMS-CF group had a first SCT of less than 40 mEq/L, in contrast to prior studies finding no children with an initial SCT ofless than 40 mEq/L transitioning to CF. Most of the CRMS-CF group had increasing SCT values before transitioning to CF, but not all reached the diagnostic threshold before genotype or clinical symptoms confirmed diagnosis. Thirty-seven percent of CRMS-CF transitioned after 6 years of age. Annual sputum culture appears warranted in children designated with CRMS given known deleterious effects of certain pathogens on the lungs of children at risk of CF. Prospective evidence-based monitoring will provide greater insight into the risk of CF in this population.

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Making cystic fibrosis community insights more accessible: An overview of the Cystic Fibrosis Foundation Community Data Repository

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Background: Community Voice is a program that enables the Cystic Fibrosis Foundation (CFF) and cystic fibrosis (CF) researchers and clinicians to tap into the lived experiences and insights of the CF community. Since it began in 2014, Community Voice has provided volunteer opportunities for community members and has shaped CF research, care, and CFF programmatic efforts. To ensure that gathering insights and lessons learned from community members is efficient and not duplicative of past research, the CFF created the Community Data Repository in 2018 to house past research on insights of the CF community, organize the research, and tag it for future use.

Methods: Previous community research and methodologies were identified and organized in chronological order. These included notes from interviews with community members, focus group reports, survey result reports, and other community data collected. Software was identified to assist in tagging efforts, and QSR International NVivo 11 for Windows was chosen to create hierarchical tagging. Two reviewers reviewed, tagged, and sorted the projects by chronological order. Tags were then categorized, consolidated, and cleaned up. More than 100 projects were tagged, most of them surveys or focus group notes. Nearly half were Community Voice projects completed from 2017 to 2022). All raw data were then organized separate from NVivo to allow open access and use for users.

Results: About one-third of tags were categorized into life with CF, more than 600 total tags. This includes research and data related to connecting with others, mental health, perceptions of CF, aging, nutrition, and reproductive health. The remaining two-thirds were sorted into four other major categories: CF complications (400+), research (300+), access (300+), and delivery of care (300+). CF complications tags included community data on complications that people living with CF face, such as pulmonary complications, gastrointestinal problems, endocrine complications, sinus complications, and aging-related problems. Research tags mostly comprised the community's perceptions of clinical trials, modulators, research prioritization, and drug discovery. Access tags included access to health insurance, health care expenses, and policy tags. Delivery of care includes community data on treatment and therapies, treatment burden, care centers, diagnosis of CF, and other complications. These five major categories make up most of the tags in the Community Data Repository. Tags related to the CFF were also created, which allows flexibility in tagging programmatic and CFF-related efforts within community data collected. An admin tag was also created to denote certain characteristics of projects, such as available segmentation or potential data cuts.

Conclusions: The Community Data Repository provides a robust look into past community research involving people living with CF and their family members. This resource is available, upon request, to CF researchers and clinicians who want to partner with the community in future projects and is also available to facilitate future engagement efforts.

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Impact of repeated non-treatment on long-term lung function

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Background: Previous findings from the Epidemiologic Study of Cystic Fibrosis (ESCF) indicated that more-consistent treatment of declines in forced expiratory volume in 1 second (FEV_1) of 10% or greater from baseline in people with CF (PwCF) was associated with better pulmonary outcomes, yet more than one-third of declines were not treated. Data are lacking from a more recent cohort and regarding the effect of repeated untreated declines. Our objective was to determine the prevalence of untreated lung function decline in a pediatric cohort and evaluate the impact of repeated nontreated decline on the probability of percentage predicted FEV_1 (FEV_1pp) recovery to 100% of baseline.
Methods: We included PwCF aged 6 to 17 followed in the Cystic Fibrosis Foundation Patient Registry between 2016 and 2019. Baseline FEV_1pp was the average of the highest three FEV_1pp recorded during a period of stability spanning 30 to 365 days. We assessed relative decreases in FEV_1pp from baseline between 2017 and 2018. Participants must have had three or more relative declines of at least 5% within a 12-month window and have had a follow-up FEV_1pp in 2019 to determine whether they had returned to baseline. Treatment within 28 days of decline was categorized as any (intravenous antibiotics, oral or inhaled antibiotics (non-intravenous antibiotics)) versus no antibiotic treatment. We defined our exposure of repeated nontreatment as 50% or more decline events not treated using any antibiotic therapy. Alternate definitions of repeated nontreatment were tested in sensitivity analyses.
Results: Four thousand eighty-eight children were reported to have three or more declines of more than 5% in a 12-month window between 2017 and 2018. We identified 2,826 (69.1%) who experienced repeated nontreatment and 1,262 (30.9%) with more than 50% of their decline events having received any antibiotic therapy within 28 days. Children who experienced repeated nontreatment had a median (interquartile range) baseline age of 11.6 years (9.2, 14.7) and baseline FEV_1pp of 96.7% (85.4, 106.0). The group for whom at least half of their declines were treated had a median age (IQR) of 13.5 years (10.1, 15.8 years) and baseline FEV_1pp of 85.9% (72.7%, 96.8%). Of the children who experienced repeated non-treatment, 35.5% returned to 100% or more of their baseline, compared with 59.7% of the children who received more frequent antibiotic treatment.
Conclusions: We found that a substantial proportion of pediatric PwCF with multiple declines of at least 5% are not being treated with antibiotic therapy, especially those with high baseline FEV_1pp. Children who experienced repeated nontreatment were younger and had more than a 10% higher baseline FEV_1pp than those who were more frequently treated with antibiotic therapy, and two-thirds did not return to baseline by the end of 2019. Next steps include modeling FEV_1pp to evaluate whether repeated nontreatment is associated with accelerated decline in lung function.

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Gingivitis in children with cystic fibrosis

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Background: The close links between the oral cavity and respiratory tract increase the potential risk of micro-aspiration of oral bacteria. Thus, it is critical to determine whether children with cystic fibrosis (CF) are at risk of oral disease. CF-related comorbidities such as diabetes, as well as systemic inflammation due to frequent lung infections and continued use of dry-mouth-inducing inhaled treatments, are potential risk factors for gingivitis (gum inflammation) [1,2]. Despite these risk factors, the current literature suggests that children with CF are at lower risk of gingivitis than those without because of chronic use of antibiotics to treat lung infections [3–5], but this literature is outdated (1977–2009) and does not account for potential confounders in the association between CF and gingivitis. Thus, the goal of this study was to compare the prevalence of gingivitis in children with and without CF.
Methods: This was a cross-sectional study comparing the risk of gingivitis in children with CF with the risk in those without CF with other special health care needs aged 7 to 17. We recruited children with CF from a single pediatric CF clinic in Seattle, Washington (n = 69) and non-CF controls from Medicaid enrollment files in Washington State (n = 89). Gingivitis was defined as bleeding in 10% or more of examined gingival sites. We used logistic regression to compare the prevalence of gingivitis between the two groups and adjusted for age, sex, race, antibiotic use, and dental insurance type as potential confounders.
Results: Children with CF were slightly younger (11.3 ± 3.1 vs 12.4 ± 2.8, $p = 0.02$), more likely to be white (93% vs 42%, $p < 0.001$), and less likely to have Medicaid insurance only (32% vs 84%, $p < 0.001$). Sixty-eight percent of children with CF and 40% of non-CF controls had gingivitis. Children with CF had significantly higher odds of gingivitis than non-CF controls (OR 3.1, 95% CI, 1.6–6.1; $p < 0.001$). This remained significant after adjusting for potential confounders (OR 4.7, 95% CI, 1.9, 11.9; $p = 0.001$).
Conclusions: In contrast to previous studies, our study showed greater likelihood of gingivitis in children with CF than in non-CF controls. Ensuring optimal oral health for children with CF is critical to maintain overall health and quality of life.
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Effect of SARS-CoV-2 on long-term physical and mental health symptoms in people with cystic fibrosis and their caregivers

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Background: SARS-CoV-2 affects people long after the acute infection has resolved, with 30% to 50% of the general population reporting persistent