A pilot retrospective longitudinal case-control study of individuals diagnosed with Cystic Fibrosis after a false-negative newborn screen

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Abstract

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Cystic fibrosis (CF) has been universally included in newborn screening (NBS) programs across the United States for nearly two decades. In Washington State, CF NBS was introduced in 2006 and follows a two-step protocol: initial immunoreactive trypsinogen (IRT) measurement, followed by limited CFTR variant analysis for samples exceeding an IRT threshold. Studies from multiple regions and countries have shown that CF NBS is associated with improved early outcomes, including enhanced nutritional status, delayed chronic *Pseudomonas aeruginosa* infection, and expedited lung function growth[1]. However, inequities persist, with Black/African American and Asian infants experiencing false-negative screens at disproportionately higher rates than non-Hispanic White infants[2]. Although false-negatives are an inherent risk of biomarker-based screening, their disproportionate burden raises concerns about systemic bias within existing NBS algorithms. To explore longitudinal clinical impacts of false-negative NBS, we conducted a pilot project assessing long-term clinical outcomes among children diagnosed with CF after false-negative NBS in WA State compared to matched peers diagnosed after positive screens. We conducted a retrospective matched case-control study of individuals born between 2006 and 2024 in WA State and followed at Seattle Children's Hospital CF Center. Cases were diagnosed after a false-negative NBS; controls were matched 1:1 by birth year (±1 year) and pancreatic sufficiency status. Data collected included demographics (birth month/year, race/ethnicity, zip code), newborn screen and diagnostic characteristics (NBS IRT level and CF

variant panel results, diagnosis month/year, CFTR genotype, clinical presentation, hospitalization status at diagnosis), and longitudinal clinical outcomes (height and weight percentiles, forced expiratory volume in one second (FEV_1) from spirometry). Additional indicators included number and duration of hospitalizations and age at first positive *Pseudomonas aeruginosa* culture. Prior analyses have suggested that individuals diagnosed with CF after a false-negative NBS may experience less favorable outcomes than matched peers, including lower weight trajectories and higher hospitalization rates.[1,3,4] Our results mirrored these patterns. False-negative cases were more racially and ethnically diverse (36.3% vs. 0%, $p = 0.027$), diagnosed later (median 19 vs. 1 month, $p < 0.0001$), and more often hospitalized at diagnosis (36.4% vs. 0%, $p = 0.045$). They also had higher annualized hospitalization rates ($p = 0.018$) and significantly slower growth trajectories. These findings suggest that false-negative NBS results may delay diagnosis and contribute to worse clinical outcomes, reinforcing concerns about equity in current screening algorithms.

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In loving memory of my dad, who taught me to wonder and isn't here to see where it led.

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I. Introduction

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive, life-shortening condition universally included in newborn screening programs across the United States. CF is caused by a mutation in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an ion channel that transports chloride and bicarbonate across the surface of epithelial cells. The reduction of membrane anion permeability in people with CF (PwCF) results in a buildup of thick, dehydrated mucus in the lungs, pancreas, and other organs. This ultimately leads to chronic respiratory bacterial infections, bronchiectasis, lung function decline and respiratory failure. In 1978, the median survival age for PwCF was 11[5]. With the advent and application of aggressive, multidisciplinary care and the recent triumph of FDA approval of highly effective modulator therapies (HEMTs), 2023 data from the CF Foundation National Patient Registry estimate the median life expectancy of infants born after 2019 to be 61 years[6].

About 85% of the CF population suffers from malabsorption due to exocrine pancreatic insufficiency (EPI), necessitating the use of supplemental pancreatic enzyme therapy (PERT). Pancreatic insufficiency in CF is linked to specific disease-causing CFTR mutations, where patients with two severe mutations are typically pancreatic insufficient from birth, require the use of PERT to facilitate growth, and are at risk of more adverse health outcomes. Those with 1 or 2 milder mutations are typically pancreatic sufficient[7].

Newborn Screening

The implementation of universal newborn screening in the United States is a great triumph in the field of population-based preventative public health programs. States have slight variations in the disorders included on NBS, but all share the imperative goal of identifying and intervening in disorders that, without prompt action, have the capacity to elicit severe consequences, including permanent disability and death.

CF is universally screened for in all 50 states, with slight variations in testing strategy both between states and over time in individual states, but the same general workflow. Immunoreactive trypsinogen, or IRT, is a pancreatic enzyme precursor known to be elevated in

the blood of most babies born with CF, although it can be elevated in babies who are just carriers of CF, or for other reasons not related to *CFTR*. Screening begins by measuring IRT level via bloodspot from a newborn heel prick. If IRT concentrations are above a certain threshold, which varies by state, a DNA panel will be run to check for common pathogenic *CFTR* mutations. The DNA panel varies by state, with Washington using a 41-variant panel. It is estimated that 90% of all individuals with CF in the U.S. have at least one copy of the most common *CFTR* pathogenic variant, F508del, but over 700 pathogenic variants have been identified[7]. *CFTR* variants vary in frequency across populations.[2] If the DNA panel detects 1 or 2 of these mutations, the positive NBS result will be relayed to the pediatrician and CF Care Center. It is important to note that there are two different ways in which CF NBS can be deemed negative – first, if IRT falls below the designated threshold, and secondly, if none of 41 variants on the DNA panel are present. For either of those situations, the screen is determined to be negative, or normal. It is known that detection rate of at least 1 *CFTR* variant on the DNA panel is highest in non-Hispanic White individuals, while Black and Asian individuals are most likely to have a false-negative screen due to lack of *CFTR* variant inclusion on the panel.[8] This presents a significant health equity concern, as current screening practices may delay diagnosis and treatment for historically underserved populations.

Universal NBS for CF was implemented in Washington state in 2006. Initially, the state followed an IRT-IRT algorithm, in which if a first IRT value was over 100 μg/L, a second IRT would be performed 7-10 days later. If this second value was over 70, the screen was considered abnormal and the infant was referred for a sweat chloride test, the gold standard diagnostic test for CF, that measures the chloride concentration in sweat. In 2019, Washington state revised the CF NBS algorithm to include lowering the IRT cutoff for both screens to 60, and adding the 41-variant panel DNA screen if either IRT concentration was above the cut-off. The most recent update occurred in 2023, when the state eliminated the second IRT screen, and now moves directly to DNA screening after a single IRT over 60[9]. Babies with CF not identified by NBS are said to have a false-negative result, which can lead to a delay in diagnosis and impact future outcomes. We know that early diagnosis of CF through newborn screening is associated with better short and long term outcomes, including nutritional parameters and potentially lung function outcomes [3,4,10].

Objectives

The objective of this project was to identify children born in Washington State and followed at Seattle Children's Hospital CF Clinic who were diagnosed with CF after a false-negative NBS and compare long-term outcomes with a matched cohort born in Washington who were identified and diagnosed from a positive NBS. Almost all children with CF are seen at CF Foundation-accredited care sites.[11] In Washington, there are four accredited sites: Seattle Children's, Mary Bridge, Madigan, and Spokane Sacred Heart. Most children with CF in Washington state receive their CF care at Seattle Children's; thus, while sample size is limited, it does encompass most children in Washington state with CF. Outcomes included nutritional status, lung function, hospitalization frequency, and age at initial acquisition of *Pseudomonas aeruginosa*, a common and significant bacterial pathogen in individuals with CF that can contribute to reduced lung function and increased risk of mortality. We hypothesized that infants who are diagnosed with CF after a false-negative NBS have adverse long-term outcomes. In addition, we hypothesized that children with a false-negative NBS are more likely to be from a minoritized background.

There are 15-25 babies born with CF every year in Washington, and an estimated 1-5 false-negative screens annually. Recognizing we are only looking at the patient pool seen at one specific hospital, we knew our sample size would be very small and not underpowered to recognize statistically significant differences in most analysis situations. Instead, this project is intended to serve as a pilot framework for future analyses of outcomes in the context of NBS in larger populations, such as the CF Foundation National Patient Registry.

II. Methods

Institutional Review Board

A protocol was submitted to and approved by the Seattle Children's Hospital Institutional Review Board. Because the research involved no more than minimal risk to research subjects and the data obtained through chart review was collected for clinical purposes unrelated to this research study, a waiver of patient consent was approved.

Cystic Fibrosis Foundation Patient Registry

This project utilized Seattle Children's electronic health record (EHR) and the Cystic Fibrosis Foundation Patient Registry (CFFPR). First introduced in 1986, the CFFPR target population is all individuals with a diagnosis of CF in the United States. CFFPR data is collected through an online portal where each CF care center uploads data for each consented patient's clinic visits, hospitalizations, and/or courses of home intravenous (IV) antibiotics. With data on over 50,000 patients, the CFFPR has enrolled an estimated over 85% of the U.S. CF patient population.[11] This comprehensive data has been used for national surveillance, quality improvement, and research, resulting in over 120 peer-reviewed publications.[12] Each site has access to its own patient data in the online database.

Eligibility criteria for cases and controls

Utilizing EHR chart review and a query report in the CFFPR, this project identified children born between January 2006 and December 2024 who were diagnosed after a false-negative NBS. For each patient diagnosed after a false-negative NBS, a CF patient born in the same year (±1 year) and of same pancreatic sufficiency status diagnosed following a positive NBS was selected as a matched control. In one case, a matched pancreatic sufficient control was not available in the year of birth. In this case, the pancreatic sufficient patient with the closest DOB was matched (approximately 3 years younger), and follow up was censored at the time of the most recent clinic visit for the case.

Several populations of patients were excluded. These included those diagnosed prenatally via amniocentesis or chorionic villus sampling (CVS) or via neonatal cord blood sampling. Up to 20% of babies born with CF present with meconium ileus (MI), which is a severe bowel obstruction at the terminal ileum due to inspissated meconium, which may or may not include intestinal perforation[13]. It is well known that MI is almost always associated with CF, meaning these babies are quickly identified to be assessed. However, MI is also associated with a lower IRT level, with up to 18.8% of these babies presenting with a normal IRT level, and thus, a false-negative NBS[14]. Because this project aims to assess the impact of delayed diagnosis due to a false-negative NBS on outcomes, these infants were excluded.

Data extracted

Data collected included demographics (birth month/year, race/ethnicity), newborn screen and diagnostic characteristics (NBS IRT level and CF variant panel results, diagnosis month/year, *CFTR* genotype, clinical presentation, hospitalization status at diagnosis), and clinical outcomes (height and weight percentiles, FEV_1). Longitudinal data was collected for the same duration for matched cases and controls. Forced Expiratory Volume in one second, or FEV_1, is a measurement of lung function from a spirometry pulmonary function test, and it is expressed as a percent of a predicted value. FEV_1 data collection began at age 6, when individuals with CF begin to perform spirometry as part of their clinic visits. Additional indicators included number and duration of hospitalizations, age at first positive *Pseudomonas aeruginosa* culture, and use of highly effective modulator therapies.

Zip code at time of diagnosis was collected to determine each individual's Childhood Opportunity Index (COI) score. COI is a composite measure of neighborhood conditions that influence children's health and development including 29 domains across three categories: education, health and environment, and social and economic factors[15]. ZIP codes at diagnosis were converted to ZCTAs, mapped to census tract GEOIDs, and linked to COI data for Washington State. The COI 2.0 (2015) scores were used for each tract.

Statistical analysis

Matched data was evaluated to identify differences and similarities in the two cohorts using a retrospective longitudinal case control study design. Patients diagnosed with CF after a false-negative NBS constituted the case cohort, with those diagnosed after a positive NBS the control cohort. Cases and control were compared using the Mann-Whitney U test for central tendencies of each phenotype.

A linear mixed-effects model was used to estimate average lung function values (FEV_1 percent predicted) over time for the false-negative NBS cohort and the positive NBS cohort. The model included fixed effects for age at encounter (continuous), NBS result (positive vs false-negative), and their interaction.

Hospitalizations and *P. aeruginosa* colonization were evaluated proportionally, comparing patients ever hospitalized versus those never hospitalized, as well as those ever colonized with *P. aeruginosa* versus those never colonized. A Chi-square test was used to detect significant differences in proportional outcomes between groups.

III. Results

While statistical analysis and cohort characteristics are presented, it is important to emphasize the *a priori* recognition that our small sample size would limit the power to detect significant associations. This data intends to serve as a framework for future analyses of longitudinal differences in CF-related outcomes following differing NBS results, with the plan of extending these methods to larger datasets (such as all babies in the state of Washington and/or the CF Foundation National Patient Registry), to assess for statistically significant differences that can reveal more structurally sound and generalizable results that might ultimately influence NBS understanding and policy.

Demographic Characteristics of the Cohorts

A total of 22 patients (9 female [40.9%]; 13 male [50.1%]) met eligibility criteria and constituted the cohort, with 11 in the false-negative NBS group and 11 in the positive NBS matched control group (Table 1). Four of the 11 false-negative NBS individuals were hospitalized at time of diagnosis. Included in the cohort were the following race and ethnicity categories: 20 White (90.1%) and 2 Asian/Middle Eastern (9.1 %), and 2 Hispanic (9.1%), and 20 Non-Hispanic (90.2%) (Table 1). All participants contributed hospitalization data, nutritional and *P. aeruginosa* outcomes, whereas 6 (27.2%) participants were too young (age <6 years) to contribute to lung-function outcomes.

Compared with the positive NBS cohort, the negative NBS cohort had a higher proportion of infants of race/ethnicity other than non-Hispanic White (4 of 11 [36.3%], vs 0 children). A Chi-square test of these proportions returned a p-value of 0.027, indicating statistical significance ($p < 0.05$). Both cohorts had identical proportions of individuals with public or no insurance versus private insurance (4 of 11 [36.3%], vs 7 of 11 [63.6%]). False-negative NBS had lower COI scores overall; however these differences were not statistically significant (Table 1).

Newborn Screen and Diagnostic Data

As expected, the positive NBS cohort had a substantially earlier median (IQR) age at diagnosis (1 [0-1]) months compared with the negative NBS cohort (19 [4.5-36]) months ($p = 6.2 \times 10^{-5*}$) (Table 1). Nine of the 11 (81.8%) false-negative NBS babies screened negative due to an IRT level falling below cutoff threshold, while 2, (18.2%) had elevated IRT but no variant detected on the 41-variant panel – both of these patients were of races other than White. One baby screened negative due to an IRT below the threshold; even if the IRT had been elevated, he would have screened negative due to no panel variants (Table 2). The positive newborn screen had a higher proportion of homozygous F508del genotypes (6 of 11 [54.5%] vs. 3 of 11 [27.3%]) (Table 3), and a lower proportion of patients with no copies of F508del (1 of 11 [9.1%] vs. 4 of 11 [36.3%])(Table 4).

No positive NBS babies was hospitalized at time of diagnosis, while 4 of the negative NBS patients were admitted at time of diagnosis, with 3 in the pediatric intensive care unit (PICU). This was a statistically significant difference ($p = 0.045$). In addition, clinical presentation at diagnosis differed between the groups. Clinical presentation at diagnosis was assessed using the CFFPR's standardized categories of clinical presentations at diagnosis (non-mutually exclusive). Most positive NBS were pre-symptomatic, with 1 presentation of electrolyte imbalance (9.1%), 1 Failure to thrive/malnutrition presentation (9.1%), and 1 Steatorrhea/abnormal stools/malabsorption presentation (9.1%), while the majority of negative NBS babies presented with Steatorrhea/abnormal stools/malabsorption 9 (81.8%) and failure to thrive/malnutrition 8 (72.7%). Four (36.4%) negative NBS babies presented with acute or persistent respiratory abnormalities.

Longitudinal Outcomes

Longitudinal data for matched cases and cohorts was collected for the same duration of time, with a median duration of follow up of 9.8 and 9.4 years for the false-negative and positive NBS, respectively. (Table 1)

Height and Weight Percentile

In linear mixed-effects models, the interaction between encounter age and NBS group was significant for both weight and height percentiles, indicating that children in the positive NBS group experienced a steeper increase in growth percentiles with age (weight: 0.86; 95% CI, 0.34

to 1.38; height: 0.52; 95% CI, 0.011 to 1.02). The main effect of NBS group was not significant for either outcome at the baseline encounter age (weight: −0.11 percentile; 95% CI, −18.20 to 17.97; height: 6.19; 95% CI, −12.23 to 24.62) (Figure 1)(Table 4).

Lung Function: Forced Expiratory Volume in the First Second of Expiration (FEV1) Predicted

A linear mixed-effects model used to estimate average lung function values (FEV_1 percent predicted) found an association between age and lung function reaching statistical significance ($\beta = -0.49$, $p = .033$), indicating a decline in FEV_1 over time for both groups. However, neither NBS status nor the interaction between NBS status and age was significantly associated with lung function (Table 4, Figure 2). This suggests no clear difference in lung function trajectory between groups in this small pilot sample.

Annual hospitalization rates and Pseudomonas Aeruginosa Colonization

There was a statistically significant difference in annualized hospitalization rate between groups, with late diagnosis patients being hospitalized at a rate about 1.8 times that of patients with a positive NBS (1.64, 0.918 [$p = 0.018$]) (Figure 2). There was no significant difference between false-negative NBS vs positive NBS in number who had ever cultured *P. aeruginosa* (4 of 11 [36.3%] vs. 5 of 11 [45.5%]). There was also no significant difference in age at initial acquisition of *P. aeruginosa* was detected by Kaplan Meier survival analysis (Figure 3).

IV. Discussion

In this small retrospective, longitudinal, matched case-control analysis of infants in WA State diagnosed with CF after a false-negative newborn screen, we observed trends and some significant differences suggesting PwCF with a negative NBS do in fact have worse outcomes. The false-negative newborn screen group was more racially and ethnically diverse than the matched controls. A statistically significant differences of 18 months was observed between age at diagnosis for false-negative NBS vs. positive NBS. Statistically significant differences were identified in the proportion of patients hospitalized at diagnosis and annualized hospitalization rate thereafter, with greater proportion and rate in the negative NBS group. Negative NBS patients were more likely to be symptomatic at time of diagnosis, and showed slower weight gain. No statistically significant difference in acquisition of *P. aeruginosa* was detected. From

the linear mixed effects model, weight at diagnosis was significantly lower in the false-negative group and rate of gain with age was significantly lower. For height, no diference was seen as baseline, but trajectory with age was significantly worse. We saw no significant differences in FEV1 percent predicted values.

Comparison with Prior Studies

Our findings of more racial and ethnic diversity amongst the false-negative screen cases is consistent with recent literature examining false-negative CF NBS cases in California, in which Asian infants with CF were more likely to have a false-negative NBS compared to non-Hispanic White infants with CF (OR 6.3, 95% CI 2.7–14.5) [2]. In a retrospective study of CF NBS in Illinois, more Hispanic infants with CF had one or more undetected mutations after screening, in comparison to non-Hispanic White patients (40% vs. 9.5%; $p < 0.002$)[16].

Prior studies have consistently shown that earlier diagnosis of CF through NBS is associated with improved outcomes, particularly regarding nutritional status in early childhood and reduced risk of severe disease presentation at diagnosis[2,10,111,7,81,3,4]. The Wisconsin Cystic Fibrosis Newborn Screening Project (CFNSP), which enrolled infants born from 1985 to 1994, randomized participants to a screened group (diagnosed in the first month) or control group (diagnosed at symptom onset or by age 4). Children in the NBS group had significantly greater weight and height percentiles at diagnosis, with differences persisting through age 18 while diminishing over time[3].

Our data and mixed-effects linear models are directionally consistent with these reports: children diagnosed after a false-negative NBS tended to have slower weight gain and were more likely to present with clinical symptoms and require hospitalization at diagnosis, though our small sample size limited the ability to detect statistically significant differences in all domains.

Implications

This pilot study suggests that children diagnosed with CF after a false-negative newborn screen experience clinically significant delays in diagnosis, more severe clinical presentations, higher hospitalization rates, and long-term adverse nutritional consequences. The overrepresentation of racially and ethnically diverse patients in the false-negative group may reflect known limitations of IRT-based screening thresholds rather than gaps in genetic panel sensitivity. Since most false

negatives in this cohort were due to low IRT values, disparities may arise from biological variation in IRT levels across populations, which current algorithms may not fully account for. While limited in scope, these findings underscore the need to examine how screening thresholds and algorithm design impact equity in early CF detection.

Limitations

This project has several limitations. As a pilot project at a single site, the small sample size limits power to detect true differences. Linear mixed effect models for nutritional and lung functions were utilized, where a more complex non-linear parametric model may be necessary to capture the true nature of the growth trajectory. While most CF patients follow a quarterly visit cadence, various structural and personal limitations mean that some patients are unable to follow this schedule, leading to variable follow up frequency.

Conclusion

Identifying disparities in longitudinal health outcomes for individuals with CF missed on NBS is an essential first step in better defining structural contributions to health inequities. There is literature comparing nutritional outcomes of children with CF before and after the implementation of NBS, but there are limited publications on initial nutritional status and growth comparing infants with positive and false-negative NBS.[1] Additional research is needed that compares long-term outcomes of children with CF diagnosed after false-negative vs. positive NBS. Identifying and understanding these health disparities is essential to highlight inequities inherent in current NBS algorithms, which will consequently motivate the development and application of more equitable newborn screening algorithms.

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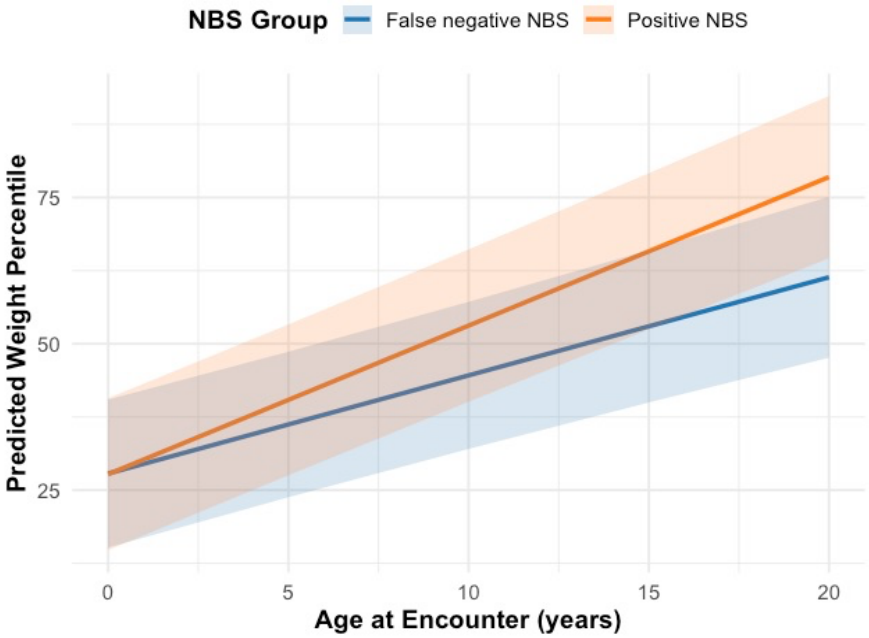
Figures

Figure 1. Association of False-Negative Newborn Screening With Observed Height and Weight Percentile and Forced Expiratory Volume in the First Second of Expiration (FEV_1) Predicted by Age and on Marginal Mean Predictions From Mixed-Effects Models

A Weight percentile by age



B Height percentile by age

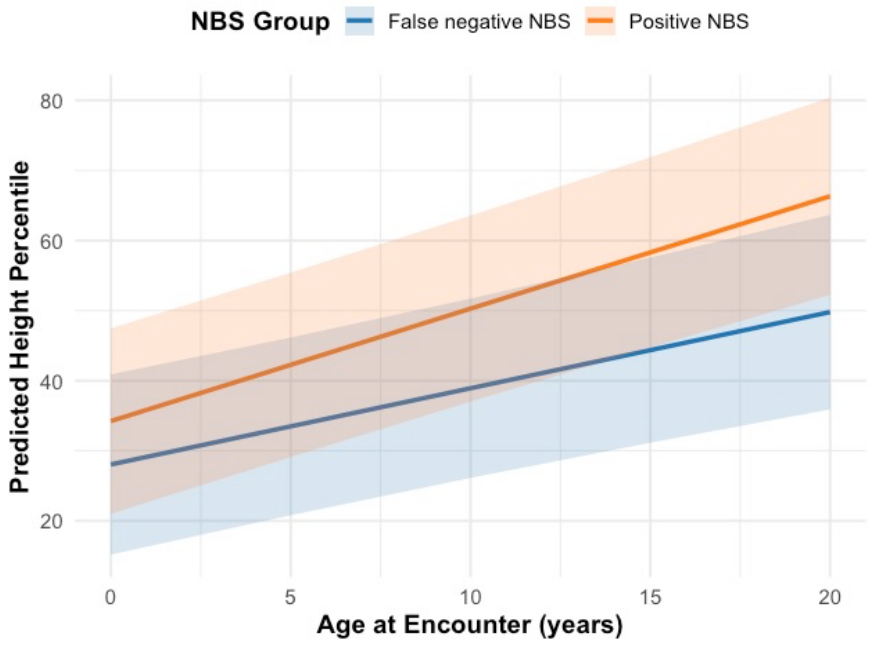


Figure 2. Association of False-Negative Newborn Screening With Forced Expiratory Volume in the First Second of Expiration (FEV_1) Predicted by Age and on Marginal Mean Predictions From Mixed-Effects Models

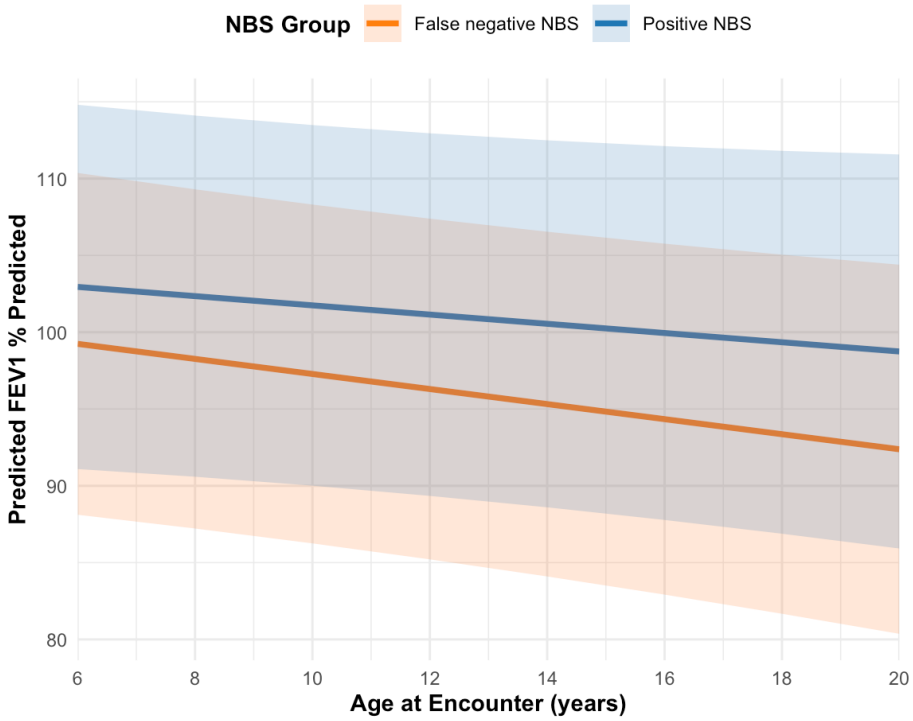
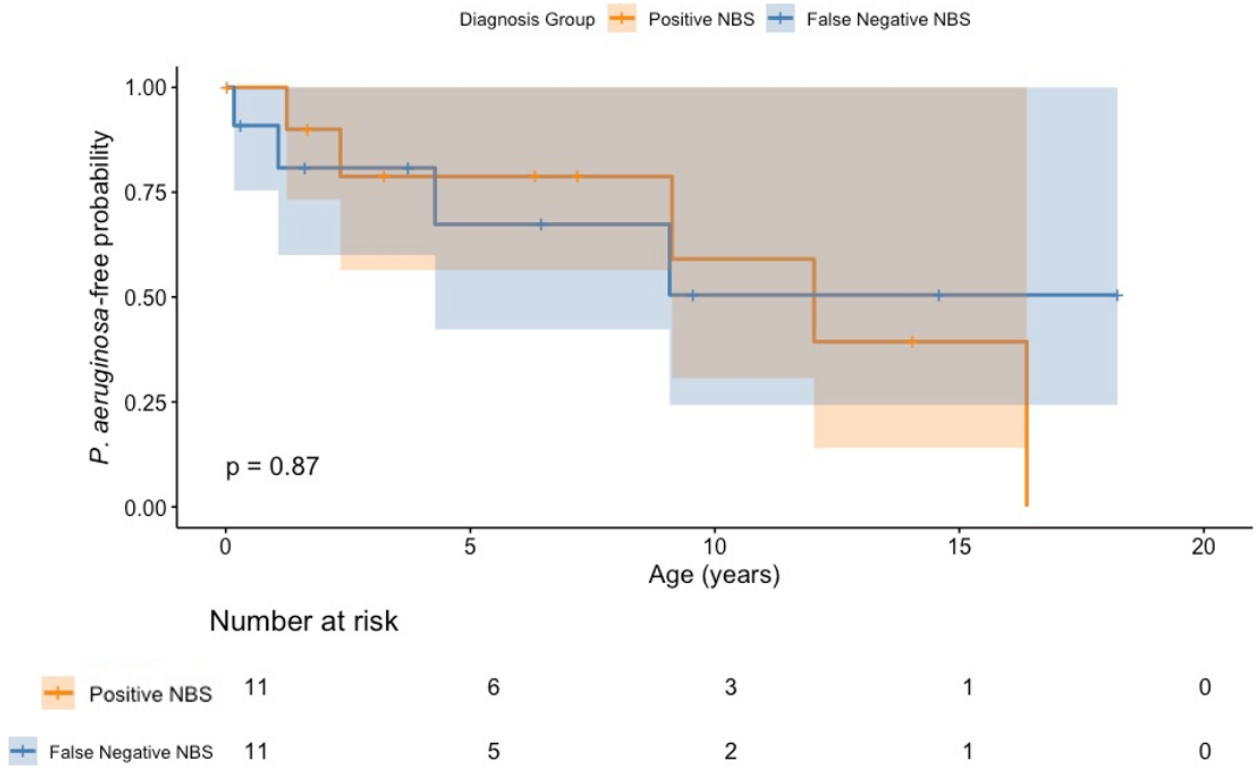


Figure 3. Kaplan-Meier Survival Analysis of initial acquisition of *Pseudomonas Aeruginosa*



Tables

Table 1. Cohort Characteristics

Characteristic	No. %		p value Mann-Whitney U Test
	False-negative NBS (n= 11)	Positive NBS (n=11)	
Sex			
Female	6 (54.5)	3 (27.2)	
Male	5 (45.4)	8 (72.7)	
Race			
White	9 (81.8)	11 (100)	
Asian/Middle Eastern	2 (18.2)	0	
Ethnicity			
Hispanic	2 (18.2)	0	
Non-Hispanic	9 (81.8)	11 (100)	
Length of follow up, years, median	9.8	9.4	
Insurance status in the year of or year following diagnosis			
Private	7 (63.6)	7 (63.6)	
Public	4 (36.3)	4 (36.3)	
Childhood Opportunity Index (median, IQR)			
Overall	73 (42,91)	78 (65,93)	$p = 0.37$
Education	76 (26,89)	78 (38,91)	$p = 0.65$
Health and Environment	82 (69,89)	91 (84,100)	$p = 0.09$
Social and Economic	69 (51,90)	80 (66,93)	$p = 0.45$

Table 2. Diagnostic and newborn screen characteristics

	No. %		
	False-negative NBS (n= 11)	Controls - Positive NBS (n=11)	p value
Age at diagnosis, mo, median (IQR)	19 (4.5,36)	1 (0,1)	$p = 6.2 \times 10^{-5}$*
Cause of false-negative NBS (%)			
IRT below cutoff	9 (81.8)		
No variants on 41-variant panel	2 (22.2)		
Hospitalized at time of diagnosis	4	0	$p = 0.045$°
at least 1 F508del *CFTR* variant, %	7 (63.6)	10 (90)	$p = 0.32$°
at least one *CFTR* variant on WA State *CFTR* variant panel (%)	8 (72.7)	11 (100)	$p = 0.21$°
no variants on WA State CFTR variant panel (%)	3 (27.2)	0	
Sweat test (mmol/mL) median, IQR	100 (80,110)	91 (65,99)	$p = 0.10$*
WA State NBS algorithm on DOB†			
IRT-IRT	8	8	
IRT-IRT-DNA	2	2	
IRT-DNA	1	1	
Presentation at diagnosis			
Acute or persistent respiratory abnormalities	4 (36.4)	0	$p = 0.09$°
Electrolyte imbalance	1 (9.1)	1 (9.1)	
Failure to thrive/malnutrition	8 (72.7)	1 (9.1)	$p = 0.0075$°
Persistent respiratory colonization/infection with a typical CF pathogen(s) (e.g., Pseudomonas aeruginosa)	1 (9.1)	0	
Pneumothorax	1 (9.1)	0	
Rectal prolapse	1 (9.1)	0	
Steatorrhea/abnormal stools/malabsorption	9 (81.8)	1 (9.1)	$p = 0.0019$°
Annualized hospitalization rate, mean	1.64	0.918	$p = 0.018$

* Mann-Whitney U Test

° Fisher's exact test

Poisson regression

† Cases and controls were matched by year of birth, yielding the same NBS algorithm breakdown

Table 3. *CFTR* genotypes by NBS Status

	Mutation 1	Mutation 2
NBS Status		
Negative	F508del	F508del
	F508del	F508del
	F508del	F508del
	F508del	N1303K
	F508del	R117H
	F508del	R117C
	F508del	N1303K
	R1158X	R1158X
	2143delT	2143delT
	1525-1G>A	1525-1G>A
	L206W	Y849X
Positive	F508del	F508del
	F508del	F508del
	F508del	F508del
	F508del	F508del
	F508del	F508del
	F508del	F508del
	F508del	R347H
	F508del	G542X
	F508del	D1152H
	F508del	c.1021_1022
	2184delA	4005+2T>C

Table 4. Weight Percentile, Height Percentile, and FEV1 Percent Predicted: Parameter Estimates From Linear Mixed-Effects Models

Parameter Estimate (95%CI)	Weight percentile	Height percentile	FEV1% predicted
Encounter age	1.68 (1.28 to 2.09)	1.09 (0.70 to 1.48)	-0.49 (-0.94 to -0.04)
Positive NBS	-0.11 (-18.20 to 17.97)	6.19 (-12.23 to 24.62)	2.57 (-14.64 to 19.78)
Encounter age × positive NBS	0.86 (0.34 to 1.38)	0.52 (0.011 to 1.02)	0.19 (-0.47 to 0.85)