

# Outcomes of Infants With Indeterminate Diagnosis Detected by Cystic Fibrosis Newborn Screening

Clement L. Ren, MD<sup>a</sup>, Aliza K. Fink, DSc<sup>b</sup>, Kristofer Petren, BS<sup>b</sup>, Drucy S. Borowitz, MD<sup>c</sup>, Susanna A. McColley, MD<sup>d</sup>, Don B. Sanders, MD, MS<sup>e</sup>, Margaret Rosenfeld, MD, MPH<sup>f</sup>, Bruce C. Marshall, MD<sup>b</sup>

## abstract

**BACKGROUND AND OBJECTIVES:** Cystic fibrosis transmembrane conductance regulator–related metabolic syndrome (CRMS) describes asymptomatic infants with a positive cystic fibrosis (CF) newborn screen (NBS) but inconclusive diagnostic testing for CF. Little is known about the epidemiology and outcomes of CRMS. The goal of this study was to determine the prevalence, clinical features, and short-term outcomes of infants with CRMS.

**METHODS:** We analyzed data from the US CF Foundation Patient Registry (CFFPR) from 2010 to 2012. We compared demographic, diagnostic, anthropometric, health care utilization, microbiology, and treatment characteristics between infants with CF and infants with CRMS.

**RESULTS:** There were 1983 infants diagnosed via NBS between 2010 and 2012 reported to the CFFPR. By using the CF Foundation guideline definitions, 1540 and 309 infants met the criteria for CF and CRMS, respectively (CF:CRMS ratio = 5.0:1.0). Of note, 40.8% of infants with CRMS were entered into the registry with a clinical diagnosis of CF. Infants with CRMS tended to have normal nutritional indices. However, 11% of infants with CRMS had a positive *Pseudomonas aeruginosa* respiratory tract culture in the first year of life.

**CONCLUSIONS:** CRMS is a common outcome of CF NBS, and some infants with CRMS may develop features concerning for CF disease. A substantial proportion of infants with CRMS were assigned a clinical diagnosis of CF, which may reflect misclassification or clinical features not collected in the CFFPR.



**WHAT'S KNOWN ON THIS SUBJECT:** Little is known about the prevalence or outcomes of infants with indeterminate diagnostic results after a positive cystic fibrosis (CF) newborn screen (CF transmembrane conductance regulator–related metabolic syndrome [CRMS]).

**WHAT THIS STUDY ADDS:** CRMS accounted for 15.7% of newborn screened diagnoses in the CF Patient Registry from 2010 to 2012 (CRMS:CF ratio = 5.0:1.0). Although most infants were healthy, some infants demonstrated clinical features concerning for CF.

<sup>a</sup>Division of Pediatric Pulmonology, Department of Pediatrics, University of Rochester, Rochester, New York; <sup>b</sup>Cystic Fibrosis Foundation, Bethesda, Maryland; <sup>c</sup>Division of Pediatric Pulmonology, Department of Pediatrics, Women and Children's Hospital of Buffalo, Buffalo, New York; <sup>d</sup>Department of Pediatrics, Northwestern University Feinberg School of Medicine and the Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; <sup>e</sup>Division of Pediatric Pulmonology, Cystic Fibrosis, and Sleep Medicine/Department of Pediatrics, University of Wisconsin, Madison, Wisconsin; and <sup>f</sup>Division of Pulmonary Medicine, Seattle Children's Hospital and Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington

Dr Ren conceptualized and designed the study, interpreted the data, and drafted the initial manuscript; Dr Fink and Mr Petren carried out the data analyses, and reviewed and revised the manuscript; Drs Borowitz, McColley, Sander, Rosenfeld, and Marshall provided input and feedback on the study design and data analyses, participated in interpretation of the data, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

[www.pediatrics.org/cgi/doi/10.1542/peds.2014-3698](http://www.pediatrics.org/cgi/doi/10.1542/peds.2014-3698)

**DOI:** 10.1542/peds.2014-3698

Accepted for publication Mar 9, 2015

Address correspondence to Clement L. Ren, MD, University of Rochester, Division of Pediatric Pulmonology, 601 Elmwood Ave, Rochester, NY 14642. E-mail: [clement\\_ren@urmc.rochester.edu](mailto:clement_ren@urmc.rochester.edu)

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

Cystic fibrosis (CF) is an autosomal-recessive condition caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene.<sup>1</sup> Early diagnosis of CF results in improved nutritional and cognitive outcomes,<sup>2,3</sup> and as of 2010 CF newborn screening (NBS) has been implemented in every state in the United States.<sup>4</sup> CF is one of the most common causes for a positive NBS test.<sup>5</sup>

In the United States, NBS programs are administered at the state level, and the specific NBS algorithm used varies from state to state.<sup>4</sup> All CF NBS algorithms begin with measurement of immunoreactive trypsinogen (IRT) from a dried blood spot. If the IRT is elevated, *CFTR* gene mutation analysis, a repeat IRT 1 to 2 weeks later, or a combination of these is performed to improve the specificity of the testing. In infants with a positive NBS, measurement of sweat chloride (Cl) is required to establish a CF diagnosis.<sup>1</sup> Like any disease-screening process, there is the potential for indeterminate results. Infants with an indeterminate diagnosis present a treatment challenge to clinicians and a stress on families. A US Cystic Fibrosis Foundation (CFF) consensus conference proposed the term CFTR-related metabolic syndrome (CRMS) to describe asymptomatic infants who have a positive CF NBS and indeterminate diagnostic testing.<sup>6</sup> Data on the prevalence, clinical features, and clinical outcomes of infants with CRMS have been limited to small retrospective single-center studies.<sup>7-9</sup>

The US CFF Patient Registry (CFFPR) added CRMS as a diagnostic category in 2010. In this report, we describe the clinical features and short-term outcomes of infants with CRMS and the accuracy of diagnostic classification of CF and CRMS in the CFFPR.

## METHODS

The design of the CFFPR has been previously described.<sup>10</sup> Every

CFF-accredited Care Center and Affiliate Program ( $n = 154$ ) participates in the CFFPR. In March 2010, the CFFPR added CRMS as a separate diagnostic category. A clinical diagnosis of CF or CRMS is entered by the care center staff for each patient. Data collected at clinical encounters include respiratory tract microbiology, growth parameters, lung function measurements, and medication use. There are some data (eg, physical examination findings) that are not entered into the CFFPR. The protocol is reviewed and approved by the local institutional review boards, and parents provide written informed consent for their child's data to be entered into the registry.

The population for this study included all patients in the CFFPR born from 2010 to 2012 whose diagnosis was entered as CF or CRMS (ie, clinical diagnosis) after a positive NBS. We also categorized infants as CF or CRMS (ie, guideline diagnosis) based on the CFF diagnostic criteria<sup>1,6</sup> by using *CFTR* mutation classifications from the Clinical and Functional Translation of *CFTR* Project (CFTR2).<sup>11-13</sup> CFTR2 has categorized mutations into 1 of 4 categories: (1) CF-causing (eg, F508del), (2) not disease causing (eg, M470V), (3) associated with varying clinical consequences (eg, R117H), and (4) unknown significance (ie, not enough information to make a clear determination).<sup>12</sup> As of July 2014, CFTR2 had evaluated 217 mutations, representing 96% of the known alleles in the CFTR2 database. In this article, we use the term unevaluated to refer to mutations for which the functional significance has not yet been evaluated. The CFF definition of CF in infants with a positive CF NBS test requires a sweat Cl  $\geq 60$  mmol/L or 2 *CFTR* gene mutations that are known to be disease causing.<sup>1</sup> CRMS is defined as infants with a positive CF NBS and either (1) a sweat Cl between 30 and 59 mmol/L and fewer than 2 CF-causing *CFTR*

mutations or (2) a normal sweat Cl ( $< 30$  mmol/L) and 2 *CFTR* mutations, of which no more than 1 is known to be CF-causing.<sup>6</sup> To derive a guideline definition of CRMS, it was necessary for patients to have adequate sweat Cl and *CFTR* mutation data to satisfy 1 of the 2 previously mentioned criteria. Also, infants with 2 unevaluated mutations were not assigned a guideline diagnosis because we could not be sure that both mutations will ultimately be found to be disease causing.

We compared the demographics (gender, race, ethnicity) of infants with a guideline diagnosis of CF with those with CRMS. In addition, for all encounters during the first year of life, we examined anthropometric characteristics, health care use, microbiology, and treatments. Differences between patients with CF and patients with CRMS and between subgroups of patients with CRMS were assessed by using  $\chi^2$  tests for categorical variables and  $t$  tests for continuous variables;  $P$  values  $\leq 0.05$  were considered statistically significant. All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC). Means and frequencies are presented with their 95% confidence intervals; nonoverlapping confidence intervals indicate significant differences with  $P < .05$ .

We conducted the following secondary analyses. First, we examined the impact of including infants born in 2012 because they did not have a complete year of follow-up. Where available, we examined the intron 8 thymidine repeat (poly T) tract status for patients whose mutation profile was F508del/R117H, as this affects penetrance (ie, R117H/5T is likely to be a disease-causing mutation, whereas R117H/7T or R117H/9T is less likely to be disease causing).<sup>12,13</sup> For infants with a positive respiratory culture for *Pseudomonas aeruginosa* (Pa), we examined the proportion of individuals with 2 or more positive cultures. Last, we examined the

association between prescription of pancreatic enzyme replacement therapy (PERT) and, where available, fecal elastase (FE) test results.

## RESULTS

From 2010 to 2012, 1983 infants diagnosed with CF or CRMS after a positive NBS were entered into the CFFPR, of whom 1731 had a clinical diagnosis of CF and 231 had a clinical diagnosis of CRMS. There were 21 infants whose clinical diagnosis was CFTR-related disorder or CF ruled out; these infants were excluded from the analysis.

Table 1 shows the distribution of the patients included in the analysis by sweat test result category and CFTR2 mutation classification and displays how we derived the guideline diagnosis. Overall, 1540 (78.5% of the cohort) met the criteria for a guideline diagnosis of CF and 309 (15.7%) met the criteria for a guideline diagnosis of CRMS. In 113 (5.8%) cases, there was insufficient sweat Cl and/or genotype data to assign a guideline diagnosis. Overall, sweat test results were not available for 19.6% of the population. Analysis of CFTR mutations in the 309 infants with a guideline CRMS diagnosis showed that 72.5% of them had 1 copy of F508del and 26% had the combination of F508del/R177H (Supplemental Table 4).

**TABLE 1** Distribution of the Sweat Cl Concentration and Genotype Results of 1962 Infants Entered Into the CFFPR as Diagnosed via NBS and Born Between 2010 and 2012

	Sweat Cl <30	Sweat Cl 30–59	Sweat Cl ≥60	Sweat Cl Missing
2 CF-causing mutations	7	50	922	303
1 CF-causing mutation and 1 unevaluated	54 <sup>a</sup>	48 <sup>a</sup>	104	21
1 CF mutation + 1 of varying consequences	85 <sup>a</sup>	83 <sup>a</sup>	14	27
1 CF mutation + 1 unknown consequences	0 <sup>a</sup>	0 <sup>a</sup>	4	1
1 CF mutation + 1 non-CF causing	14 <sup>a</sup>	6	2	5
Both mutations evaluated but neither CF causing	12 <sup>a</sup>	7 <sup>a</sup>	3	2
Both mutations unevaluated	4	1	11	1
Not genotyped	1	0	38	13
Genotyped but <2 mutations recorded	11	14	82	12

<sup>a</sup> Infants meeting the guideline diagnosis of CRMS. The total number of guideline diagnosis CF infants was 1540 and with CRMS was 309. For 113 infants there was insufficient information to assign a diagnosis

Comparing the guideline diagnosis with the clinical diagnosis (Table 2), almost all patients with a guideline diagnosis of CF also had a clinical diagnosis of CF. In contrast, 40.8% of patients with a guideline diagnosis of CRMS had a clinical diagnosis of CF. Among patients for whom we had insufficient information to assign a guideline diagnosis, 64.6% had a clinical diagnosis of CF.

Table 3 displays the demographic characteristics, health utilization, nutritional and pulmonary outcomes, and treatments prescribed in infants with a guideline diagnosis of CF compared with those with a guideline diagnosis of CRMS. Infants with CRMS were significantly more likely to be nonwhite (African American, Asian, Native American, or mixed race), there was a nonsignificant increase in the percentage of infants who were Hispanic, and they had significantly higher anthropometric measures with a mean weight-for-length percentile above the 50th percentile. Infants with CRMS were seen on average 3.8 times within the first year of life and had oropharyngeal swabs obtained on average 2.6 times, significantly fewer than infants with CF. At least 1 positive Pa respiratory culture was recorded in 10.7% of infants with CRMS as compared with 20.9% of infants with CF ( $P < .05$ ). Among infants with CF, 76.2% were

**TABLE 2** Comparison of Clinical Diagnosis (Entered Into CFFPR by Site) Versus Analytic Diagnosis (Based on CFF Guidelines)

	Analytic Diagnosis			Total
	CF	CRMS	Unknown	
Clinical diagnosis				
CF	1532	126	73	1731
CRMS	8	183	40	231
Total	1540	309	113	1962

Infants in the unknown category had insufficient data in the CFFPR to assign an analytic diagnosis.

prescribed PERT as compared with 7.8% of infants with CRMS ( $P < .05$ ). Overall, infants with CRMS were significantly less likely to be prescribed CF treatments. To assess whether sweat Cl concentration was associated with different clinical features or outcomes, we compared infants with CRMS with a sweat Cl <30 mmol/L with those with sweat Cl of 30 to 59 mmol/L. We found no significant differences between these 2 groups (Supplemental Table 5).

Among infants with a guideline diagnosis of CRMS, those with a clinical diagnosis of CF had significantly more clinic visits and cultures than those with a clinical diagnosis of CRMS (Supplemental Table 6). Growth parameters did not differ substantially between the groups. There was a nonsignificant trend toward more cultures that were positive for Pa and other CF-associated airway pathogens among infants with a clinical diagnosis of CF. Infants with a clinical diagnosis of CF were significantly more likely to be prescribed CF-related therapies, especially PERT and dornase alfa but less likely to be prescribed bronchodilators.

We conducted several secondary analyses to assess the robustness of our data and gain further insight into the results. Because the study included data from January 1, 2010, to December 31, 2012, infants born in 2012 did not have a full year of data

**TABLE 3** Characteristics of Infants With Analytic Diagnoses of CF Versus CRMS

	CF	CRMS
<i>n</i>	1540	309
Girls, %	49.5 (47.0–52.0)	48.9 (43.3–54.4)
Nonwhite, % <sup>a</sup>	6.5 (5.3–7.7)	12.3 (8.6–16.0)
Hispanic, %	12.6 (10.9–14.4)	18.7 (10.7–25.5)
Health care use, mean		
No. of visits	7.7 (7.4–7.9)	3.8 (3.4–4.1)
No. of cultures	4.9 (4.8–5.1)	2.6 (2.4–2.9)
Anthropometric measurements, mean		
Height percentile	33.7 (32.5–35.0)	52.0 (49.0–55.1)
Weight percentile	30.9 (29.7–32.2)	53.0 (49.8–56.3)
Weight for length percentile	43.8 (42.6–45.1)	54.1 (50.9–57.2)
Microbiology, % with ≥1 positive cultures		
Pa	20.9 (18.9–22.9)	10.7 (7.2–14.1)
<i>S aureus</i>	53.6 (51.1–56.1)	43.0 (37.5–48.6)
<i>S maltophilia</i>	13.6 (11.9–15.3)	9.4 (6.1–12.6)
<i>H influenzae</i>	22.2 (20.2–24.4)	15.2 (11.1–19.2)
Treatments, %		
PERT	76.2 (74.1–78.4)	7.8 (4.8–10.8)
Inhaled antibiotic	7.5 (6.2–8.8)	4.2 (2.0–6.5)
Dornase alfa	29.7 (27.4–32.0)	4.2 (2.0–6.4)
Bronchodilators	68.6 (66.3–70.9)	30.4 (25.3–35.6)
Supplemental oral feeding	32.2 (29.9–34.6)	8.7 (5.6–11.9)

Numbers in parentheses represent 95% confidence intervals.

<sup>a</sup> Nonwhite represents African Americans, Asians, Native Americans, and infants of mixed race.

entered into the CFFPR. Therefore, we performed an analysis excluding infants born in 2012. Not surprisingly, infants with a complete year of data had a higher total number of encounters and cultures. However, similar to infants with a complete year of data, infants with CF were seen more often and had more cultures compared with infants with CRMS.

There were 115 infants with the F508del/R117H mutation profile, 89 with a guideline diagnosis of CRMS and 26 with a guideline diagnosis of CF. Poly T tract data were available for 57.3% of these infants. Among those with poly T tract data, 9.8% were 5T, 78.4% were 7T, 3.9% were 9T, and the remainder was unknown.

Among the 309 patients with CRMS, 89 (28.8%) infants had a single respiratory tract culture recorded during the first year of life, and 220 infants (71.2%) had >1 culture. Pa was reported in 5 (5.6%) of the infants with only 1 culture. Among the 220 patients with more than 1 culture, 21 (9.5%) had 1 positive

Pa culture. An additional 7 infants (3.2%) had ≥2 positive cultures.

FE test results were available on 43% of the total cohort. Among infants with a guideline diagnosis of CRMS, 9.1% were prescribed PERT and half of them had an FE level ≤200 µg/g as compared with 74.1% of patients with a guideline diagnosis of CF prescribed PERT, 93.9% of whom had an FE level ≤200 µg/g.

## DISCUSSION

CF is one of the most common causes of a positive NBS test, and in some cases follow-up testing results in an indeterminate diagnosis, creating a stressful situation for families and caregivers. Using data from the CFFPR, we have provided the largest, most comprehensive description of CRMS ever reported. For the first time, we also have provided detailed short-term outcome data on CRMS from a national data set. We found that some infants with CRMS have Pa (a pathogen strongly associated with CF) cultured from their respiratory tract. Our findings will be useful to

clinicians and families who are confronted with indeterminate diagnostic results after a positive CF NBS test. We also observed a difference between the clinical and guideline diagnoses of infants with CRMS with a substantial proportion (40.8%) of infants with a guideline diagnosis of CRMS classified by clinicians as having CF. Our results point out the diagnostic challenges in classifying infants who come to clinical attention through NBS.

Parad et al<sup>14</sup> were among the first to describe infants with positive CF NBS and indeterminate diagnostic testing. Since then, there have been a limited number of reports about CRMS, but they have been small studies that frequently have not focused on clinical outcomes.<sup>7</sup> Ren et al<sup>8</sup> reported their experience with a small cohort (*n* = 12) of infants with CRMS at a single CF center, and Sermet-Gaudelus et al<sup>9</sup> studied outcomes in CF NBS-positive infants with and without abnormal nasal potential difference measurements. In both studies, there were infants with CRMS who developed features of CF disease. However, the small number of patients studied limited their ability to estimate the incidence of these outcomes and how applicable their findings were to the general population of infants with CRMS. Our study population comes from >100 CF centers across the country, and provides a more comprehensive picture of CRMS in the United States.

Our results indicate that infants with CRMS in general demonstrate normal growth and nutrition, but may have laboratory tests that are concerning for manifestations of CF. Although *Staphylococcus aureus* and *Haemophilus influenzae* can be found in the respiratory tract of infants without CF, the incidence of Pa and *Stenotrophomonas maltophilia* in the first year of life in the CRMS cohort was much higher than that

reported in non-CF populations.<sup>15,16</sup> However, data on the prevalence of these CF-related pathogens in individuals without CF are somewhat limited, and we could not assess the clinical consequences of positive Pa oropharyngeal cultures in this study. We also cannot determine if follow-up of these infants at the CF center potentially exposed them to CF patients who were Pa-positive and contributed to their acquiring Pa in their respiratory tract. Although FE levels were not recorded for all the infants with CRMS in the CFFPR, analysis of the available data suggests that some infants with CRMS may have pancreatic insufficiency and thus have a symptom consistent with a diagnosis of CF or transiently impaired pancreatic function, which does not require lifelong treatment with PERT.<sup>17</sup>

Our data show that there are differences in demographics and treatment between infants with CRMS with a normal sweat Cl, 1 disease-causing CFTR mutation, and 1 mutation of uncertain or variable significance (47% of the guideline diagnosed CRMS cohort) compared with infants with CRMS with an intermediate sweat Cl concentration. However, both groups showed a greater than expected prevalence of Pa-positive respiratory cultures, suggesting that risk of acquiring Pa may be higher in infants with CRMS than in the general population regardless of their sweat Cl concentration and emphasizing the need for good infection-prevention strategies.<sup>18,19</sup> A common genotype identified in our study was F508del/R117H, a finding that also has been reported in other studies of CRMS.<sup>8,9</sup> Among those with poly T data available, similar to previous studies, we found that 7T was the most common polymorphism identified in infants with CRMS. Although R117H with 7T is considered unlikely to act as a disease-causing mutation, in some cases it can be associated with clinical symptoms of CF.<sup>4,12,13,20-22</sup>

Our results demonstrate that a diagnosis of CRMS is a relatively common outcome of CF NBS. Infants with CRMS accounted for 15.7% of NBS infants entered into the CFFPR, and the ratio of CF to CRMS cases was 5.0:1.0. Our analysis probably underestimates true CRMS prevalence, as CF centers are not required to enter infants with CRMS into the CFFPR and may not be entering their data into the CFFPR. Also, some families may not consent to participation in the CFFPR. Although the overall prevalence of CRMS was 15.7%, this is likely to vary by state because of differences in the NBS algorithm. Of note, the proportion of non-white and Hispanic infants was higher in the CRMS group compared with the CF group. This may be because IRT levels are higher in African American neonates compared with white infants,<sup>23-25</sup> resulting in a higher proportion of positive NBS tests. The higher percentage of Hispanic infants in the CRMS group may be related to the use of CFTR gene sequencing in California, a state with a large Hispanic population.<sup>26</sup>

There are several limitations to our study. There was incomplete information for some data elements, in particular sweat Cl concentration, poly T status, and FE levels, which may have biased some of our results. For example, the absence of FE data made it difficult to determine if patients were being appropriately treated for pancreatic insufficiency. Even if available, a single FE value may be hard to interpret, because in some instances initially normal FE results may decline and low values may increase to be in the normal range in the first year of life.<sup>17,27</sup> Missing data have been reported before in other CF patient registries.<sup>28</sup> Through global collaboration in projects such as CFTR2, the clinical significance of the most common CFTR mutations has been determined.<sup>11,12</sup> Although some

mutations have yet to be fully characterized, this is unlikely to have a significant impact on our results, because they do not account for most positive CF NBS tests. Our analysis showed that 40.8% of the infants with a guideline diagnosis of CRMS received the clinical diagnosis of CF. Differences in classification of infants with CRMS might have resulted from misinterpretation of the CFF guidelines,<sup>29</sup> reliance on NBS as a diagnostic test, or clinical data not captured in the CFFPR that led clinicians to categorize these infants as CF. It also may reflect reluctance among CF clinicians to accept the use of CRMS as a diagnostic category. In 113 infants (5.8% of the cohort) there was insufficient sweat Cl and/or genetic data to assign a diagnosis, highlighting the importance of having complete genetic and sweat Cl data to accurately assign a diagnosis of CF.

## CONCLUSIONS

We have conducted the largest multicenter study to date of the clinical features and initial outcomes of infants with CRMS. CRMS is a common outcome arising from CF NBS, and although the vast majority of infants with CRMS are healthy, a small proportion of them may develop manifestations of CF. Our results will be helpful to clinicians who need to counsel and care for infants with CRMS and their families. They also support the CFF CRMS guidelines, which recommend that these infants should be monitored for the development of clinical features of CF,<sup>6</sup> although good infection-control practices should be in place to avoid potentially increasing their risk for Pa acquisition. Education of CF clinicians on the CF and CRMS definition and a follow-up consensus conference on diagnosis and treatment of CF and CRMS also should be considered to address issues of potential misclassification.

**FINANCIAL DISCLOSURE:** Drs Fink and Marshall and Mr Petren are employees of the Cystic Fibrosis Foundation. Dr Sanders reports grants and personal fees from the Cystic Fibrosis Foundation during the conduct of the study. The other authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** The Cystic Fibrosis Foundation provided support for this study.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**COMPANION PAPER:** A companion to this article can be found on page e1377, online at [www.pediatrics.org/cgi/doi/10.1542/peds.2014-2081](http://www.pediatrics.org/cgi/doi/10.1542/peds.2014-2081).

## REFERENCES

- Farrell PM, Rosenstein BJ, White TB, et al; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008; 153(2):S4–S14
- Farrell PM, Kosorok MR, Laxova A, et al; Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med*. 1997;337(14): 963–969
- Farrell PM, Kosorok MR, Rock MJ, et al; Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics*. 2001; 107(1):1–13
- Wagener JS, Zemanick ET, Sontag MK. Newborn screening for cystic fibrosis. *Curr Opin Pediatr*. 2012; 24(3):329–335
- Wadsworth Center. New York Department of Health. Newborn Screening Program Annual Reports. Available at: [www.wadsworth.org/newborn/annualrept/annsum.htm](http://www.wadsworth.org/newborn/annualrept/annsum.htm). Accessed August 15, 2014
- Borowitz D, Parad RB, Sharp JK, et al; Cystic Fibrosis Foundation. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. *J Pediatr*. 2009;155(suppl 6): S106–S116
- Narzi L, Ferraguti G, Stamato A, et al. Does cystic fibrosis neonatal screening detect atypical CF forms? Extended genetic characterization and 4-year clinical follow-up. *Clin Genet*. 2007;72(1): 39–46
- Ren CL, Desai H, Platt M, Dixon M. Clinical outcomes in infants with cystic fibrosis transmembrane conductance regulator (CFTR) related metabolic syndrome. *Pediatr Pulmonol*. 2011; 46(11):1079–1084
- Sermet-Gaudelus I, Girodon E, Roussel D, et al. Measurement of nasal potential difference in young children with an equivocal sweat test following newborn screening for cystic fibrosis. *Thorax*. 2010;65(6):539–544
- FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr*. 1993;122(1):1–9
- Castellani C; CFTR2 team. CFTR2: how will it help care? *Paediatr Respir Rev*. 2013;14 (suppl 1):2–5
- Sosnay PR, Siklosi KR, Van Goor F, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet*. 2013;45(10):1160–1167
- The Clinical and Functional Translation of CFTR (CFTR2). Home page. Available at: <http://cftr2.org>. Accessed March 4, 2015
- Parad RB, Comeau AM. Diagnostic dilemmas resulting from the immunoreactive trypsinogen/DNA cystic fibrosis newborn screening algorithm. *J Pediatr*. 2005;147(suppl 3):S78–S82
- Carlson D, McKeen E, Mitchell M, et al. Oropharyngeal flora in healthy infants: observations and implications for cystic fibrosis care. *Pediatr Pulmonol*. 2009; 44(5):497–502
- Rosenfeld M, Bernardo-Ocampo C, Emerson J, Genatossio A, Burns J, Gibson R. Prevalence of cystic fibrosis pathogens in the oropharynx of healthy children and implications for cystic fibrosis care. *J Cyst Fibros*. 2012;11(5):456–457
- Walkowiak J, Herzig KH. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. *Eur J Clin Invest*. 2001;31(5):425–430
- Kosorok MR, Jalaluddin M, Farrell PM, et al. Comprehensive analysis of risk factors for acquisition of *Pseudomonas aeruginosa* in young children with cystic fibrosis. *Pediatr Pulmonol*. 1998;26(2): 81–88
- Saiman L, Siegel JD, LiPuma JJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infect Control Hosp Epidemiol*. 2014;35 (suppl 1):S1–S67
- O’Sullivan BP, Zwerdling RG, Dorkin HL, Comeau AM, Parad R. Early pulmonary manifestation of cystic fibrosis in children with the DeltaF508/R117H-7T genotype. *Pediatrics*. 2006;118(3): 1260–1265
- Ren CL. Pulmonary manifestations in deltaF508/R117H. *Pediatrics*. 2007;119(3): 647–648
- Thauvin-Robinet C, Munck A, Huet F, et al; Collaborating Working Group on R117H. The very low penetrance of cystic fibrosis for the R117H mutation: a reappraisal for genetic counselling and newborn screening. *J Med Genet*. 2009;46(11):752–758
- Giusti R; New York State Cystic Fibrosis Newborn Screening Consortium. Elevated IRT levels in African-American infants: implications for newborn screening in an ethnically diverse population. *Pediatr Pulmonol*. 2008; 43(7):638–641
- Gregg RG, Simantel A, Farrell PM, et al. Newborn screening for cystic fibrosis in Wisconsin: comparison of biochemical and molecular methods. *Pediatrics*. 1997;99(6):819–824
- Rock MJ, Mischler EH, Farrell PM, Bruns WT, Hassemer DJ, Laessig RH. Immunoreactive trypsinogen screening for cystic fibrosis: characterization of infants with a false-positive screening test. *Pediatr Pulmonol*. 1989; 6(1):42–48

26. Prach L, Koepke R, Kharrazi M, et al; California Cystic Fibrosis Newborn Screening Consortium. Novel CFTR variants identified during the first 3 years of cystic fibrosis newborn screening in California. *J Mol Diagn.* 2013;15(5):710–722
27. O'Sullivan BP, Baker D, Leung KG, Reed G, Baker SS, Borowitz D. Evolution of pancreatic function during the first year in infants with cystic fibrosis. *J Pediatr.* 2013;162:808–812.e1
28. Thomas M, Lemonnier L, Gulmans V, et al. Is there evidence for correct diagnosis in cystic fibrosis registries? *J Cyst Fibros.* 2014;13(3):275–280
29. Parad RYC, Sontag M. CFTR Related metabolic syndrome (CRMS) definitions: evaluating use by CF clinicians and newborn screening programs. *Pediatr Pulmonol.* 2013;48:384

## Outcomes of Infants With Indeterminate Diagnosis Detected by Cystic Fibrosis Newborn Screening

Clement L. Ren, Aliza K. Fink, Kristofer Petren, Drucy S. Borowitz, Susanna A. McColley, Don B. Sanders, Margaret Rosenfeld and Bruce C. Marshall  
*Pediatrics* 2015;135:e1386

DOI: 10.1542/peds.2014-3698 originally published online May 11, 2015;

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/135/6/e1386">http://pediatrics.aappublications.org/content/135/6/e1386</a>
<b>References</b>	This article cites 26 articles, 6 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/135/6/e1386#BIBL">http://pediatrics.aappublications.org/content/135/6/e1386#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Genetics</b> <a href="http://www.aappublications.org/cgi/collection/genetics_sub">http://www.aappublications.org/cgi/collection/genetics_sub</a> <b>Pulmonology</b> <a href="http://www.aappublications.org/cgi/collection/pulmonology_sub">http://www.aappublications.org/cgi/collection/pulmonology_sub</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.aappublications.org/site/misc/Permissions.xhtml">http://www.aappublications.org/site/misc/Permissions.xhtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.aappublications.org/site/misc/reprints.xhtml">http://www.aappublications.org/site/misc/reprints.xhtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Outcomes of Infants With Indeterminate Diagnosis Detected by Cystic Fibrosis Newborn Screening**

Clement L. Ren, Aliza K. Fink, Kristofer Petren, Drucy S. Borowitz, Susanna A. McColley, Don B. Sanders, Margaret Rosenfeld and Bruce C. Marshall

*Pediatrics* 2015;135:e1386

DOI: 10.1542/peds.2014-3698 originally published online May 11, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/135/6/e1386>

Data Supplement at:

<http://pediatrics.aappublications.org/content/suppl/2015/05/07/peds.2014-3698.DCSupplemental>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

