Effects of Immediate Telephone Follow-Up with Providers on Sweat Chloride Test Timing after Cystic Fibrosis Newborn Screening Identifies a Single Mutation

Alison La Pean, MS, CGC[1], Michael H. Farrell, MD[1], Kerry L. Eskra, MS[1,2], and Philip M. Farrell, MD, PhD[3]

Objective To assess whether reporting "possible cystic fibrosis (CF)" newborn screening (NBS) results via fax plus simultaneous telephone contact with primary care providers (PCPs) versus fax alone influenced 3 outcomes: undergoing a sweat chloride test, age at sweat chloride testing, and undergoing sweat testing before age 8 weeks.

Study design This was a retrospective cohort comparison of infants born in Wisconsin whose PCP received a telephone intervention (n = 301) versus recent historical controls whose PCP did not (n = 355). Intervention data were collected during a longitudinal research and quality improvement effort; deidentified comparison data were constructed from auxiliary NBS tracking information. Parametric and nonparametric statistical analyses were performed for group differences.

Results Most infants (92%) with "possible CF" NBS results whose PCP lacked telephone intervention ultimately underwent sweat testing, underlining efficacy for fax-only reporting. Telephone intervention was significantly associated with improvements in the infants undergoing sweat testing at age ≤6 weeks and <8 weeks and a slight, statistically nonsignificant 3.5-day reduction in the infants' age at sweat testing. The effect of telephone intervention was greater for PCPs whose patients underwent sweat testing at community-affiliated medical centers versus those whose patients did so at academic medical centers (P = .008).

Conclusion Reporting "possible CF" NBS results via fax plus simultaneous telephone follow-up with PCPs increases the rate of sweat chloride testing before 8 weeks of age, when affected infants are more likely to receive full benefits of early diagnosis and treatment. *(J Pediatr 2013;162:522-9)*.

All US states, and many countries worldwide, test for cystic fibrosis (CF) as part of routine newborn screening (NBS) using infant blood spots collected shortly after birth. Testing methods for CF vary across NBS programs, but all begin with analysis for elevated immunoreactive trypsinogen (IRT) and end with a confirmatory sweat chloride test for a large subset of infants with abnormal IRT results. In this study, we investigated how telephone follow-up with primary care providers (PCPs) influences the timing of sweat chloride testing.

In Wisconsin, NBS for CF is a 2-tiered process beginning with IRT analysis of all blood spot samples. Samples with elevated IRT undergo targeted genetic analysis for 23 mutations in the CF transmembrane conductance regulator (CFTR) gene, *CFTR*. The most commonly reported abnormal result is "possible CF,"[1] which denotes elevated IRT and the presence of a single *CFTR* mutation. The Cystic Fibrosis Foundation recommends that all infants with this type of abnormal CF screening result undergo sweat chloride testing by pilocarpine iontophoresis because of the residual possibility of having CF caused by the presence of a second mutation not included in the NBS mutation panel.[2,3] Wisconsin data suggest that these infants have a 2%-5% chance of having CF diagnosed through an abnormal sweat chloride test, and that sweat chloride testing should be done by 8 weeks of age for infants to receive the full benefits of early diagnosis and treatment.[4-8]

For timely sweat chloride testing to occur, NBS laboratories must ensure that abnormal results reach a PCP who will take responsibility for informing the parent and ensuring that the infant undergoes a sweat chloride test. However, there is no consensus regarding the protocols for reporting and follow up after "possible CF" NBS results, possibly because each NBS program is responsible for determining its own protocols for each geographic locale.[9-12] Reporting and follow-up procedures vary but can include any combination of the following methods for reporting results[9,11,12]: fax, telephone, certified letter, regular mail, and e-mail. Many NBS programs employ nurses and other allied health professionals contact families directly, whereas other programs defer such contact entirely to clinicians or support groups.[13-15]

CF	Cystic fibrosis
CFTR	CF transmembrane conductance regulator
COR	Clinician of record
FTE	Full-time equivalent
IRT	Immunoreactive trypsinogen
NBS	Newborn screening
PCP	Primary care provider

From the [1]Center for Patient Care and Outcomes Research, Medical College of Wisconsin, Milwaukee, WI; [2]Department of Rehabilitation Psychology and Special Education, School of Education, and [3]Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, WI

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The usual mechanism for Wisconsin's NBS laboratory to report "possible CF" NBS results is by fax to PCPs, followed by a copy of the results sent via regular mail. Additional contact with PCPs is not routine but may occur, via follow-up letter or telephone, to explore reasons for delays in sweat chloride testing when the NBS laboratory has not received notification of testing. The primary goal of the present analysis was to assess whether reporting of "possible CF" NBS results via fax plus simultaneous telephone contact with PCPs versus fax alone affected the following 3 sweat chloride testing outcomes: undergoing a sweat chloride test, age at the time of sweat chloride testing, and undergoing a timely sweat chloride test (before age 8 weeks). Another secondary, post hoc analysis was conducted to determine whether the 3 sweat chloride testing outcomes were influenced by any other factors, such as the center at which sweat chloride testing was performed.

Methods

This secondary analysis using a subset of data from a larger project[16] is a retrospective cohort comparison of infants whose PCP received an immediate telephone intervention versus recent historical controls from the previous 2 years whose PCP did not receive the intervention. The telephone intervention was done as part of a longitudinal statewide research study and quality improvement effort, the Wisconsin Project on Improvement of Communication Processes and Outcomes after Newborn Screening ("the project"). This project is a collaboration of the Wisconsin State Laboratory of Hygiene and the Department of Health Services, with the Medical College of Wisconsin as a contracted agent. Project methods are described in more detail elsewhere.[16] The project was approved by Institutional Review Boards at the Medical College of Wisconsin and University of Wisconsin–Madison.

NBS Laboratory Protocol for Reporting Abnormal CF NBS Results

The Wisconsin NBS program began CF screening in 1985 (on a research basis) and incorporated it into routine practice for all newborns in 1994, using the IRT-DNA (F508del mutation only) method. In 2002, the laboratory replaced single (F508del) mutation screening with a multiple mutation panel of 25 *CFTR* mutations, which was slightly reduced to 23 *CFTR* mutations in 2008 in accordance with American College of Medical Genetics and Genomics recommendations[17] (which did not affect the timing, reporting, or accuracy of CF NBS), with an estimated sensitivity of 97%.[18] The NBS laboratory's usual practice is to fax and mail a copy of abnormal CF NBS results indicating elevated IRT and a single *CFTR* mutation to the clinician of record (COR) listed on the NBS card. Infants with abnormal results indicating elevated IRT and 2 *CFTR* mutations (affected) prompt a fax plus immediate phone call to the COR, whereas infants with a highly elevated IRT (≥170 ng/mL) with no *CFTR* mutation identified have results reported by mail. The focus of this analysis is on follow-up of patients with elevated IRT, single *CFTR* mutation NBS results only.

The NBS laboratory also performs auxiliary tracking of abnormal CF NBS results to verify sweat chloride testing dates, sweat chloride testing sites, chloride levels, and resulting diagnoses. Wisconsin lists 5 CF referral centers for sweat chloride testing on all abnormal CF NBS reports. Four of these 5 medical centers receive faxes of every abnormal CF NBS result in the state, and 1 center requested not to receive these faxes. In addition, all 5 medical center's CF clinic is faxed a "summary report" every 1-2 weeks listing all of the infants with abnormal CF results in the state that year, with specific NBS results and space for the clinic to update sweat chloride test information. The CF clinic faxes the updated summary report back to the NBS laboratory within a few days, the laboratory updates its records, and the cycle continues. Medical centers other than those listed on the abnormal CF NBS report do not typically receive the individual abnormal CF results or the faxed summary report, and usually convey sweat chloride test results by phone to the NBS laboratory.

If there is no record of an infant's sweat chloride test by age 8 weeks, the NBS laboratory sends a reminder letter to the COR. If there is still no record of a sweat chloride test and the COR has not contacted the NBS laboratory with further information, then a representative of the NBS laboratory phones the COR to reiterate the need for sweat chloride testing. A COR who is not the infant's PCP must make a good faith attempt to identify the infant's PCP or convey the results to the family himself or herself. At any point, the NBS laboratory may be informed by the COR that he or she is not an infant's PCP, cannot find the PCP, or cannot reach the family. In those cases, the NBS laboratory pursues the case more aggressively (by calling the hospital of birth or having a public health nurse or social worker attempt to contact the family directly). The NBS laboratory continues to follow-up on infants with belated sweat chloride tests for up to 12 months, or until sufficient information is gathered to engender confidence that the infant's need for sweat chloride testing is known by a responsible PCP and that testing will eventually occur. The NBS laboratory performs this follow-up, regardless of the project intervention (so that the intervention group and the nonintervention group received the same level of NBS laboratory follow-up at the same time points), and thus is unlikely to have biased either cohort.

Source of Data and Recruitment for the Intervention Group

As part of the project, the NBS laboratory faxed NBS results to the project team at the same time they did so to the COR. Infants who had NBS results indicating elevated IRT with a single *CFTR* mutation and were born within the 24-month period from December 2007 to November 2009 were included in the project. Infants with reported abnormal NBS results for more than one condition, gestational age <35 weeks, and calendar age >180 days at the time of specimen collection were excluded. Other exclusion criteria included spending more than 5 days in the hospital or neonatal intensive care unit, rehospitalization after discharge from the nursery, undergoing evaluation for another serious medical