

## Newborn Screening for Cystic Fibrosis in Delaware

Ambika Shenoy, MD;<sup>1</sup> Kathi Peeke, APN;<sup>2</sup> Kathryn Tullis, PhD<sup>3</sup>; Michael Cellucci, MD;<sup>4</sup> Aaron Chidekel, MD<sup>5</sup>

1. Pediatric Pulmonologist; Associate Director, Cystic Fibrosis Center, Nemours/Alfred I. DuPont Hospital for Children
2. Advanced Practice Nurse; Nurse Coordinator, Cystic Fibrosis Center, Nemours/Alfred I. DuPont Hospital for Children
3. Program Administrator, Newborn Screening Program, State of Delaware
4. Pediatrician, Division of Diagnostic Pediatrics, Nemours/Alfred I. DuPont Hospital for Children
5. Pediatric Pulmonologist; Director, Cystic Fibrosis Center, Nemours/Alfred I. DuPont Hospital for Children

### Overview

A four-month-old female was admitted to the hospital with severe failure to thrive and diffuse macular rash. Additional symptoms included abdominal distension and colicky pain along with frequent emesis. Respiratory symptoms were absent. Screening bloodwork to evaluate failure to thrive was unrevealing and medical management for gastroesophageal reflux was unsuccessful. Upon admission to the hospital, height and weight were below the 5th percentiles for age. Sweat chloride testing was obtained on hospital day 3, confirming the diagnosis of Cystic Fibrosis (CF). Comprehensive management resulted in improved nutritional status and resolution of the rash, which was attributed to nutritional zinc deficiency. Her hospital stay lasted 15-days.

An eighteen-month-old male was admitted to the hospital for evaluation of recurrent bronchiolitis and worsening noisy breathing. Chronic cough had been present for several months and attributed to recurrent viral respiratory tract infections. A trial of bronchodilator therapy was unsuccessful. No prior history of pneumonia was reported and chest radiography on admission was negative for infiltrate. Growth and developmental parameters were normal. Pulmonology and Otolaryngology consultations were requested on hospital day 4. Due to ongoing noisy breathing, a combined airway evaluation with flexible and rigid bronchoscopy was scheduled. Upon entering the airway, copious purulent secretions were noted to be filling the tracheal and bronchial lumens. After the procedure, the patient required intensive care unit admission due to respiratory distress. Broad-spectrum antibiotics were started and bacterial cultures were positive for *Pseudomonas aeruginosa*. Once stable enough to undergo sweat chloride analysis, this test confirmed the diagnosis of CF. Comprehensive management was initiated with clinical improvement. His hospital stay lasted 18-days.

A three-week-old male infant was evaluated in Cystic Fibrosis Clinic due to a newborn screen for CF consistent with this diagnosis. An initial Immunoreactive Trypsinogen (IRT) was abnormal at 89ng/mL and the repeat IRT value was further increased at 166ng/mL. In addition, CF-gene mutation analysis revealed two copies of the most common CF-causing mutation: F508del.

The infant was asymptomatic, but had not yet regained his birthweight. Confirmatory sweat chloride testing and genotype analysis were performed. Comprehensive CF care and multidisciplinary family support was implemented with prompt acceleration of weight gain and the infant has remained healthy over the ensuing months.

Newborn screening (NBS) for CF has revolutionized the diagnosis and early management of this common, inherited disease. The goal of NBS for CF is to allow for the initiation of comprehensive, CF-specific medical and psychosocial therapies in pre-symptomatic infants with this disease. This is in stark contrast to the situation prior to the availability and implementation of NBS, when patients with CF would present symptomatically, most often with persistent respiratory symptoms, failure to thrive or both. These symptomatic presentations could be severe or even devastating in nature or subtle and puzzling, resulting in prolonged periods of evaluation and testing before a diagnosis of CF was confirmed.

Termed “diagnostic odysseys” these difficult journeys have largely been eliminated by newborn screening. NBS for CF and its impact on the early diagnosis, management and outcomes for children and families affected by this disease is nothing short of a public health triumph.<sup>1</sup>

## **Cystic Fibrosis: An Introduction to the Disease and its Common Features**

CF is one of the most common life-shortening genetic conditions, seen in approximately 1 out of every 3500 live births per year in the United States. While CF occurs with greater frequency in the Caucasian population, it is described in people of all ethnic, genetic and cultural backgrounds. Table 1 lists common clinical symptoms described in patients with CF.

Table 1. Common clinical manifestations of Cystic Fibrosis upon initial presentation in children

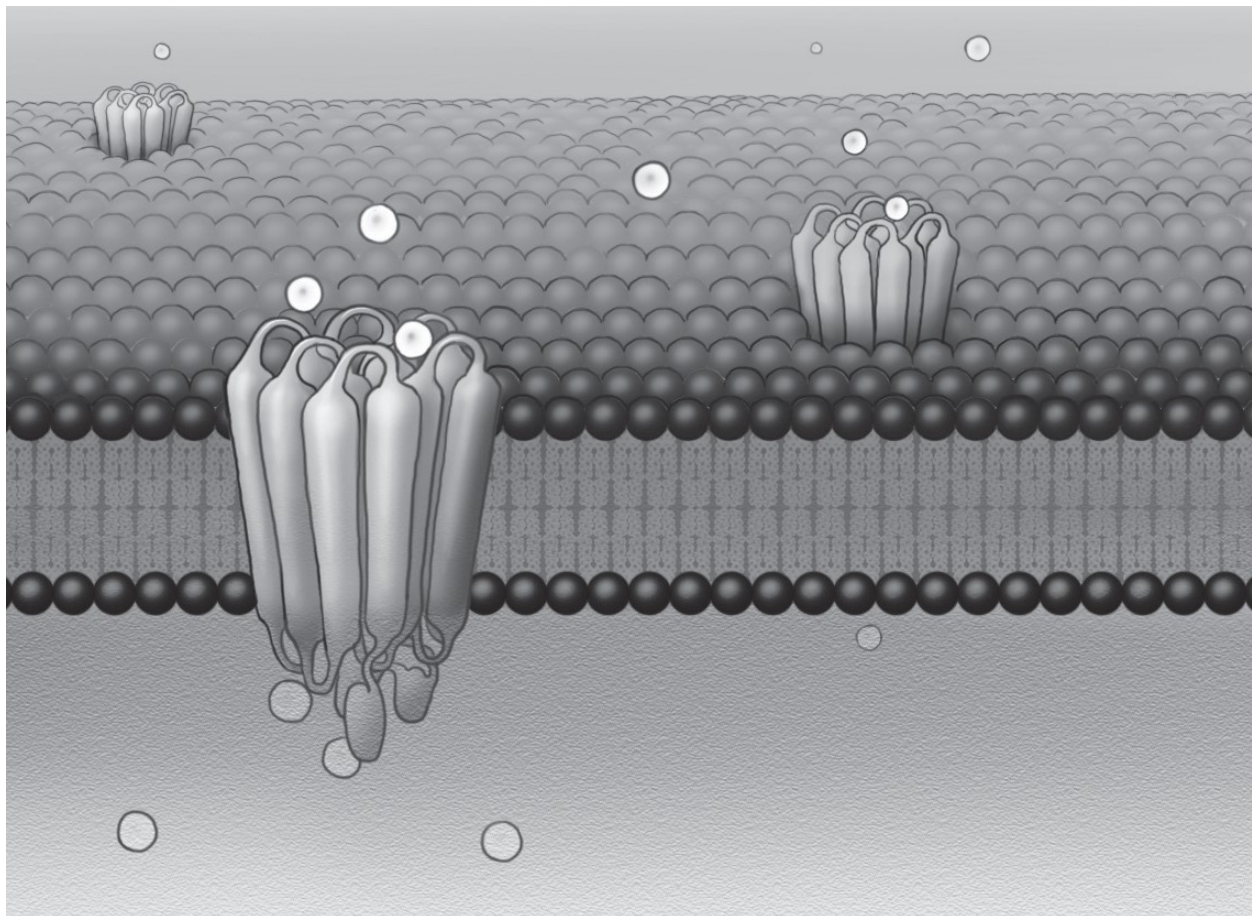
Respiratory	Recurrent respiratory infections Obstructive lung disease Chronic mucopurulent cough Nasal polyposis (especially in young children) Chronic sinusitis
Gastrointestinal/ Nutrition	Growth disturbances/Failure to thrive Malnutrition due to exocrine pancreatic insufficiency Fat soluble vitamin (A, D, E, K) deficiencies Pancreatitis Meconium ileus Bowel obstruction
Metabolic	Electrolyte imbalances/Increased insensible salt loss Salt depletion (particularly in infants) Metabolic Alkalosis

These clinical characteristics occur as the result of mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. CF is an autosomal recessive disease that results from mutations in a single CF- gene located on chromosome 7. Despite this overt simplicity, the actual genetics of CF are extremely complex and multidimensional, and a full discussion of this complexity is beyond the scope of this review. For example, over 1800 mutations have been described in the CFTR gene, but only approximately 10-15% of these mutations have been shown to cause CF disease. Furthermore, the clinical significance of many

CFTR gene mutations or variants is incompletely understood, and this occasionally results in diagnostic uncertainty. It has also necessitated the development of newborn screening strategies that are more involved than simply testing for CF-gene mutations.<sup>2</sup>

The CF gene encodes the CFTR protein, a chloride channel found on the apical membrane of epithelial cells; most notably in the respiratory tract, gastrointestinal tract and the sweat gland (see Figure 1). Due to the absence of chloride secretion and subsequent hyperabsorption of sodium, mucus and/or secretions in the CF respiratory or gastrointestinal epithelia are dehydrated. In the CF airway, tenacious, inspissated mucus is difficult to clear, prone to infection and causes cyclical airway obstruction, ongoing inflammation and ultimately gradual decline in lung function. Premature death, most commonly due to respiratory failure, is the result of this vicious cycle.

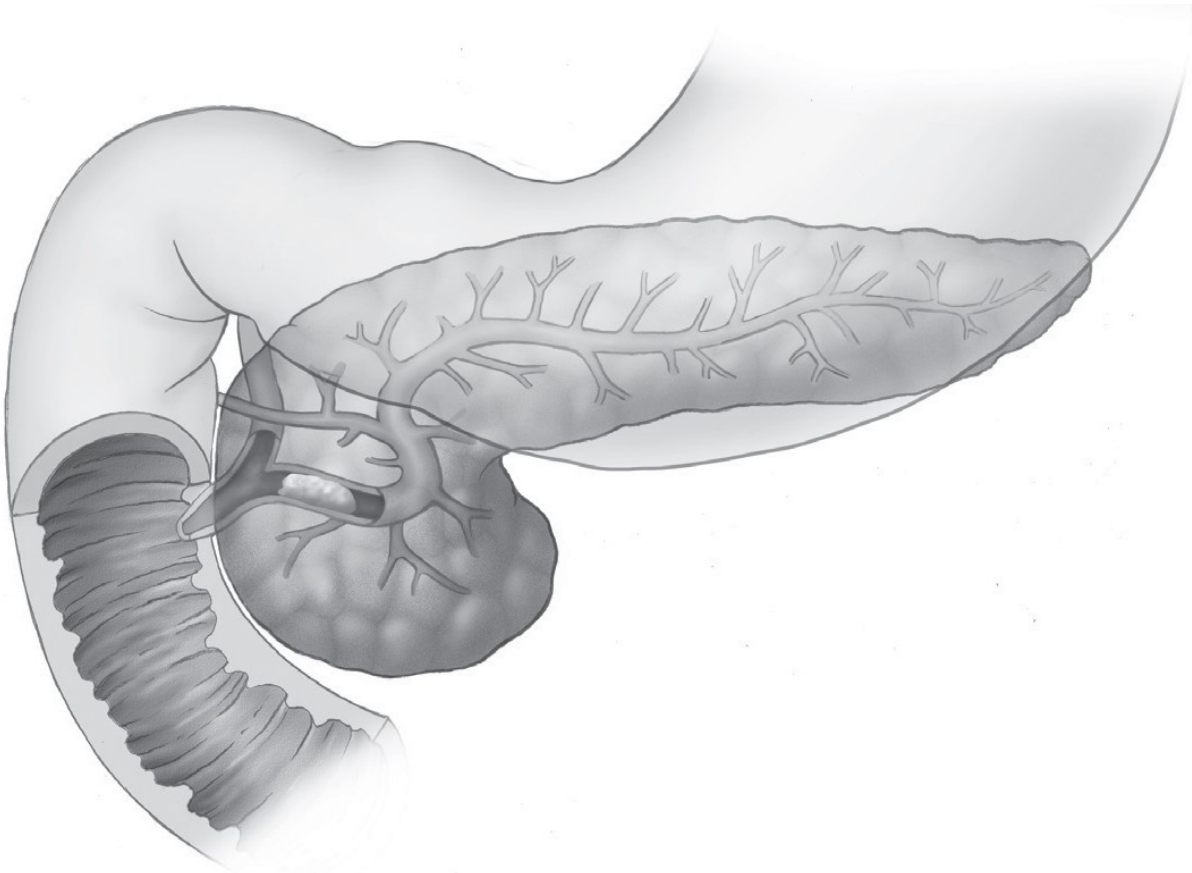
Figure 1. Chloride ions move from inside to outside a cell through the CFTR protein channel



In the gastrointestinal tract, inspissated mucus in the pancreatic ducts (even before birth) results in exocrine pancreatic insufficiency accounting for the original description of patients with this disease: “Cystic fibrosis of the pancreas” by Dorothy Anderson in 1938.<sup>3</sup> Inability of the pancreas to secrete digestive enzymes results in steatorrhea (loose, greasy or fatty, malodorous, bulky stools) with poor weight gain and lack of linear growth (see Figure 2). Inspissated mucus in the intestinal tract combined with exocrine pancreatic insufficiency with partially digested gastrointestinal contents may cause meconium ileus (at birth) or intestinal obstruction following the perinatal period. CFTR protein in the sweat glands is important for reabsorption of chloride

secreted by integumentary epithelia for temperature regulation. CF patients experience increased insensible salt losses, increased sweat chloride concentration and are at higher risk for dehydration and electrolyte disturbances, particularly in infants.<sup>4</sup>

Figure 2. Digestive enzymes from the pancreas are blocked and do not make it into the small intestine.



The diagnosis of CF is based on the presence of clinical symptoms in combination with diagnostic testing. Historically, clinical symptoms would bring an individual to medical attention for this testing, as seen in the first two clinical cases described earlier. In the era of newborn screening for CF however, it is most often a positive NBS for CF that brings a minimally or even asymptomatic infant to medical attention for further testing and confirmation of the presence or absence of CF. The diagnosis of CF requires both clinical manifestations as well as direct evidence of CFTR absence or dysfunction. Evidence for the former (clinical manifestations) is provided by an abnormal NBS; an elevated IRT, which may indicate CF-related pancreatic dysfunction. Evidence of CFTR dysfunction is confirmed by performing a sweat chloride test to demonstrate an elevated sweat chloride concentration that confirms an absence of functional CFTR in the sweat gland. The Cystic Fibrosis Foundation requires sweat testing on all infants with CF as a criterion for inclusion in the national CF Patient Registry. The evaluation for presence of two CF gene mutations that are known to cause CF is additional testing that is performed in patients.<sup>5</sup>

With the implementation of widely available, state-sponsored NBS programs, approximately 64% of infants with CF are diagnosed within the first month of life and prior to the development

of clinical symptoms of CF (apart from meconium ileus).<sup>2</sup> Early diagnosis helps decrease development of clinical symptoms such as frequent, severe respiratory infections, growth failure and malnutrition, or electrolyte disturbances. Early diagnosis also allows for the timely initiation of CF therapies including airway clearance, pancreatic enzyme replacement therapy, salt supplementation and more aggressive antimicrobial therapies in the setting of infections. Early intervention with these therapies provides the opportunity to potentially improve quality of life, stabilize decline in lung function, improve growth and electrolyte imbalances and have improved life expectancy from the teens in the 1970s to >40 years as of 2017.<sup>2</sup>

## **CF Newborn Screening: Testing**

Nationwide newborn screening for CF commenced in 2010 following strong endorsements by US Centers for Disease Control in conjunction with the Cystic Fibrosis Foundation.<sup>2</sup> Many states were including CF in their NBS programs prior to this time. NBS for CF in Delaware began in 2007. The CF NBS screening strategy utilized by each state depends on varying factors including NBS programs already in place (i.e. 1 or 2 bloodspot), cost of testing, local CF expertise and recommendations, and concern for identifying asymptomatic CFTR mutation carriers. NBS for CF meets all of the requirements of an efficacious screening test in terms of its sensitivity, specificity and positive (or negative) predictive value, although these will vary slightly depending upon the precise newborn screening protocol employed.<sup>6</sup> False negative tests, while reported, are quite rare.<sup>7</sup>

All screening tests in the United States primarily utilize measurements of IRT as the first tier or indicator of positive screening. The IRT is a protein marker of pancreatic inflammation/disease. This is typically elevated in most patients with CF. Determining if IRT is elevated varies by state program and may include top percentage of IRT values on the day of testing versus an absolute cut-off for elevation which is based on the normal distribution of IRT values occurring within the individual state.<sup>8</sup> Regardless of strategy used to measure IRT, elevation of initial IRT typically triggers a second tier of testing. Some states, may retest IRT levels (known as IRT/IRT). Typically these states, utilize two-tier NBS already and therefore, the second IRT level is drawn from blood with the second NBS around 14 days of life. The strategy is to determine if IRT is persistently elevated as is typical in patients with CF. The benefits of this methodology may include lower cost and lower carrier rate detection. However, challenges include: ensuring early notification that initial IRT is elevated, appropriate ordering and completion of the second IRT testing, in addition to the frequent need for confirmatory sweat testing. The IRT/IRT screening strategy is declining due to risk of missed diagnoses from false negatives or concerns about lack of follow-up. There are very few states that currently employ this screening strategy.

To further improve the sensitivity and specificity of CF NBS, and to decrease the need for confirmatory sweat testing, most states adopted a testing strategy combining IRT measurements with testing for common CF-causing mutations. These IRT-DNA or IRT/IRT-DNA strategies are similar in principle and all require additional testing after an initially elevated IRT result on the first screen.

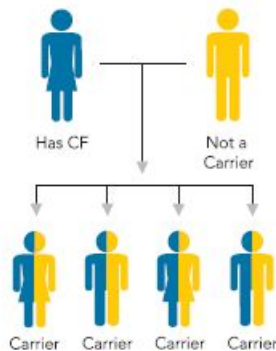
Some states will repeat the IRT screen and if still elevated, proceed to additional DNA testing (known as IRT/IRT/DNA). More commonly, many states forgo second-round IRT testing and proceed directly to DNA testing when the initial IRT is elevated (known as IRT/ DNA). An important exception is the infant with an “ultrahigh IRT” level on the initial blood spot. This result is considered significant enough to warrant referral for sweat testing. Similar to the

variability in IRT testing strategies, states may also use various CF DNA mutation panels. The DNA testing panel (run upon initial blood spot) may screen only for a single CFTR mutation- F508del (formerly called DeltaF508)- 1 copy is found in ~80% of patients with CF, or employ a combination panel including between ~ 23-43 mutations/variants in the CFTR gene.<sup>9</sup> Even less commonly, some states will perform CFTR full gene analysis.

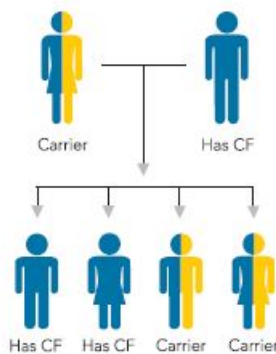
Delaware uses a combination of these modalities. If the initial IRT is elevated, a CFTR mutation panel of approximately 40 mutations/variants is screened on the first bloodspot and a second IRT level is drawn with the second blood spot while DNA is being processed. Utilization of DNA testing improves sensitivity and specificity of diagnosing patients with abnormal NBS with CF. However, it also increases the rate of identifying CF mutation carrier state if a CF-causing mutation is identified on NBS (see Figure 3). Genetic counseling or visit with CF specialist should be offered to patients with abnormal CF NBS in combination with the need for diagnostic testing. At present, our CF NBS strategy is being reevaluated with input from the Nemours-Alfred I. duPont for Children CF Center in combination with State of Delaware NBS program.

Figure 3. How a Person Gets CF

To have CF, you must get one copy of the CF gene from each parent. If one parent has CF, and the other parent is not a CF carrier all the children will be carriers.



When one parent has CF and one parent is a carrier, there is a 50 percent chance of having a child with CF.



Newborn screening for CF can be challenging and it should be noted that it only represents a screen. Infants identified as demonstrating a positive NBS for CF, require a diagnostic evaluation with sweat chloride testing at a Cystic Fibrosis Foundation and CLABSI-accredited laboratory. Infants delivered in setting of perinatal stress, hypoglycemia, low Apgar scores, congenital anomalies in addition to certain ethnic backgrounds may demonstrate elevated IRT in the absence of CF. These infants may still require sweat chloride testing to determine if the screen was falsely positive (in the absence of other clinical signs or symptoms of CF). Additionally, infants with CF manifesting with meconium ileus, may demonstrate low IRT levels and may not demonstrate positive CF NBS. Infants with meconium ileus, regardless of NBS results should undergo confirmatory CF-testing with sweat chloride and/or CFTR genotype analysis to provide a diagnosis and avoid a falsely negative screen given that clinical symptoms of CF are already present.<sup>8</sup> NBS does not replace clinical judgment by care providers; diagnostic testing should be pursued in patients with symptoms concerning for CF regardless of NBS results. Other challenges of CF NBS may include parental anxiety about the possibility of a genetic disease in their healthy appearing neonate or misunderstanding about test results. Candid discussion about test results, rationale for additional testing, and genetic counseling by CF knowledgeable caregivers is helpful in these situations.

## **Evaluation of an Infant with Positive Newborn Screen**

Most infants identified with a positive NBS for CF do not have the disease, but rather have a false positive NBS. Some additional infants are identified as CF carriers, as stated previously. All infants with a positive NBS for CF require confirmatory testing with sweat chloride analysis. This situation is associated with family stress and medical complexity. The Cystic Fibrosis Center at the Nemours/Alfred I. duPont Hospital for Children is committed to evaluating infants with positive CF NBS results accurately, efficiently and supportively so that the status of each affected infant can be defined, and their families counseled appropriately.

The involvement of the CF Center begins when Center staff, most often the Advanced Practice Nurse (APN) Coordinator, is contacted by the Delaware NBS Program about an infant with a positive screen. Four general groups of infants are evaluated in our program depending upon the State of birth and testing strategy employed: Infants with ultrahigh IRT, infants with persistently elevated IRT, infants with elevated IRT and one identified CF-gene mutation and infants with elevated IRT and two identified CF-gene mutations.

The NBS Program contacts the CF Center within 1-2 days of abnormal results. Once a member of the CF team is contacted, a telephone call is made to the infant's primary care provider (PCP) to determine if they have received the results and have spoken with the family. After discussion with the PCP confirming the discussion of an abnormal NBS result requiring a sweat chloride testing, the CF APN Coordinator will contact the family. The discussion with the family includes: sweat chloride testing instructions, scheduling of the sweat chloride test and an appointment with a physician member of the CF team the same day as the sweat test. Table 2 lists strategies for optimizing yield of the sweat test. Additional topics of discussion include providing information about CF, assessing parental CF-gene carrier status, the presence of other siblings in the family, and an assessment of the status of the infant with the positive NBS. Salt supplementation may be started in select infants. The family is also provided the Cystic Fibrosis Foundation ([www.cff.org](http://www.cff.org)) website if they request more information regarding CF, but it is also stressed that most infant sweat test results (~90%) are negative.



Table 2. Optimizing Yield of Sweat Chloride Testing

Ensure	Patient is afebrile and well-hydrated Minimum infant weight of ~2.5-3.5 kg is met
Avoid Testing If...	Creams/lotions or other skin care products have been applied to the forearms 24-72 hours prior to testing Cutaneous rash is present on forearms Critical or severe illness is present Electrolyte disturbance is present

Sweat chloride testing must be performed at an accredited Cystic Fibrosis Care Center. Despite this, sweat chloride testing in infants can be challenging and it is critical that the strategies in Table 2 be shared with the family to maximize the chances of obtaining an adequate test. The sweat test is scheduled Monday through Thursday at the outpatient lab of the Nemours/ Alfred I. duPont Hospital for Children and the appointment with the CF physician occurs later the same day. At the appointment with the CF physician, the results of the sweat test are reviewed and questions about the Newborn Screening process and results answered in person and in detail. Most often, this simply involves reporting a negative sweat test result and reassuring the family. Parents of infants who have been identified as CF carriers are counselled about this clinical finding. In cases where the sweat test is insufficient or the results are indeterminate, additional clinical assessment of the infant, counselling and follow up testing is scheduled.

Finally, if the infant has a positive sweat chloride indicating that the infant indeed has CF, comprehensive and multidisciplinary care and family support can be provided.<sup>10</sup>

During the past year (2017), 36 infants from Delaware and surrounding states have been evaluated through this clinical process. Four infants were confirmed to have CF, two infants have had indeterminate testing and are being monitored clinically and the remainder of the infants had false positive newborn screen results. Of these 30 infants, with false positive NBS results, 19 were identified as carrying one copy of an abnormal CF-gene. Therefore, in this small population of infants with positive CF NBS, the false positive rate was 83% (30/36), the true positive rate was 11% (4/36) and in 6% (2/36) of infants CF has not yet been able to have

CF confirmed or ruled out. This last group of infants are a recognized group who require additional testing and follow up to define their clinical status, and a certain percentage of these infants will go on to be confirmed to have CF over time.<sup>11</sup>

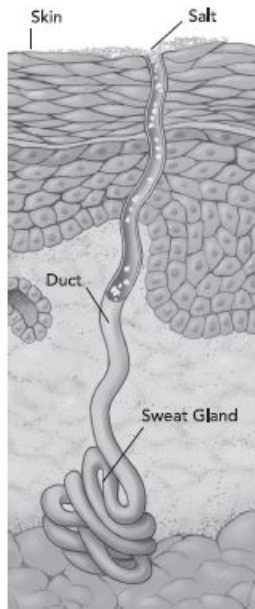
## Diagnostic Testing: Sweat Chloride Measurements

Sweat chloride testing or “pilocarpine iontophoresis” is the gold standard test for diagnosing CF.<sup>12</sup> This process directly measures CFTR function in the sweat duct (see Figure 4).

Fortunately, it does not require any needles or bloodwork. The test takes approximately sixty minutes. During the test, pilocarpine, a cholinergic agonist, is applied to the forearms and low current electrodes are attached to stimulate sweat production. The sweat volume is collected in discs and chloride concentration calculated by trained technicians.

Figure 4. Sweat Chloride Testing





Sweat produced in a person with CF has a very high level of salt.

As previously mentioned, it is imperative that sweat chloride testing be completed in CFF and CLABSI-accredited laboratories. The Nemours- Alfred I. duPont Hospital for Children is the only such laboratory in the state of Delaware. Depending on the methodology, adequate sweat volume (of at least 15  $\mu\text{L}$ ) is required in order to report reliable test results. Regardless of age, sweat chloride values greater than or equal to 60 mmol/L are consistent with CF and require repetition on a second day for confirmation.<sup>13</sup> In infants less than 6 months of age, sweat chloride values less than 30 mmol/L make possibility of CF unlikely. There are very rare cases of patients in whom CF is diagnosed with sweat chloride levels less than 30mmol/L. In patients less than 6 months of age, sweat chloride values between 31-59 mmol/L are indeterminate and require repetition. If values on follow-up testing are still in the indeterminate range, additional testing with CFTR gene mutational analysis is indicated by two months of age with follow-up sweat chloride testing suggested again around 6 months of age.<sup>2</sup>

## Outcomes

NBS diagnosis for CF allows for earlier therapeutic intervention. Infants identified early by NBS with CF and pancreatic insufficiency who initiated high calorie diet and pancreatic enzyme replacement therapy demonstrated improved growth compared with CF infants with delayed diagnosis upon onset of clinical symptoms. In a randomized clinical trial, growth parameters (height, weight, head circumference) were significantly greater for CF infants with early diagnosis (NBS) when compared with a control group of later diagnosis upon onset of clinical symptoms.<sup>14</sup> Furthermore, these anthropometric differences between early and late-diagnosis CF infants remained apparent into early childhood and adolescence despite both groups being maintained on similar higher calorie diet and pancreatic enzyme replacement therapy. This suggests that earlier diagnosis and initiation of disease- specific therapy impacts later childhood growth. It also supports the idea that “catch-up” growth is difficult following severe malnutrition observed in symptomatic CF infants. This study also suggested that non-NBS CF infants demonstrated Vitamin E deficiency compared with CF NBS identified infants. Vitamin E

deficiency was thought to negatively impact cognitive development. The Baby Observational and Nutrition Study (BONUS) demonstrated that CF infants identified by NBS also achieved normal predicted weight in the first year of life compared with age-matched infants without CF.<sup>15</sup> Achievement of weight for length greater than or equal to the 50<sup>th</sup> percentile for age at 2 years, is associated with improved baseline lung function in childhood compared with CF patients with weight for length less than the 50<sup>th</sup> percentile.<sup>16</sup> Therefore, establishing normal growth and stable nutritional status in early childhood also impacts later lung function for patients with CF.

Spirometric values obtained in school-aged children diagnosed by NBS suggest lung function preservation and significantly better lung function compared with CF patients diagnosed later upon onset of symptoms.<sup>17</sup> In an Australian cohort, patients with CF diagnosed by NBS demonstrate increased lung function compared with non-NBS counterparts even into adolescence<sup>18</sup> while other studies have not identified persistent spirometric improvements.<sup>19</sup> The current US data published in the 2016 Cystic Fibrosis Foundation Annual Patient Registry Report<sup>20</sup> supports overall normal lung function in school-aged and pre-teen patients with CF.

CF infants diagnosed by NBS exhibited decreased rates of hospitalization compared with those diagnosed upon onset of symptoms. CF patients with later diagnosis typically required hospitalization for respiratory-related symptoms earlier and for greater length of stay.<sup>21</sup> There did not appear to be differences in rates of hospitalization for gastrointestinal manifestations.

## Summary

In conclusion, the diagnosis of CF earlier through NBS detection helps to identify and treat infants early and prior to severe manifestations of disease and improves overall outcomes. Patients diagnosed with CF following NBS, demonstrate reduced rate and duration of respiratory hospitalizations. They also demonstrate better nutritional status and overall more stable, improved lung function. Furthermore, early identification offers benefits for family members including education about the disease, earlier initiation of therapy and also genetic counseling. Lastly, patients may also benefit from initiation of disease, genetic mutation-specific therapies which have become available in the last 4-5 years which may also impact the trajectory of CF-manifestations.

Collaboration between the state NBS program and local CF team is also important to ensure that all infants with CF are appropriately identified and given the best possible opportunity for a healthy start.

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