Newborn screening for cystic fibrosis

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Purpose of review
Newborn screening for cystic fibrosis (CF) is now universal in the US and many other countries. The rapid expansion of screening has resulted in numerous publications identifying new challenges for healthcare providers. This review provides an overview of these publications and includes ideas on managing these challenges.

Recent findings
Most CF newborn screening algorithms involve DNA mutation analysis. As screening has expanded, new challenges have been identified related to carrier detection and inconclusive diagnoses. Early descriptions of infants with CF-related metabolic syndrome (CRMS) indicate that the natural history of this condition cannot be predicted. Early identification has also provided an opportunity to better understand the pathophysiology of CF. However, few studies have been conducted in infants with CF to determine optimal therapy and recommendations are largely anecdotal.

Summary
Newborn screening provides an opportunity to identify and begin treatment early in individuals with CF. Whereas a single, optimal approach to screening does not exist, all programs can benefit from new findings regarding sweat testing, carrier detection, early pathophysiology, and clinical outcomes.

Keywords
CFTR related metabolic syndrome, cystic fibrosis, immunoreactive trypsinogen, mutation analysis, newborn screening

INTRODUCTION

The US reached a milestone in 2010 when Texas established a newborn screening (NBS) program for cystic fibrosis (CF), making screening universal across all 50 states and the District of Columbia. This achievement followed the statement by the Centers for Disease Control (CDC) in 2004 that universal newborn screening for CF was justified based on the long-term benefits from early nutritional treatment [1]. Additionally, the majority of parents support the value of newborn screening and have encouraged states to institute universal screening programs [2]. However, with universal CF screening new issues have arisen. Multiple different CF screening protocols exist, although most include genetic mutation analyses. Choice of protocol is often based on the balance between the risk of false-negative results and the added costs of managing false-positive results. Genetic testing necessarily includes asymptomatic carrier detection, which newborn screens for other diseases generally do not include. Additionally, some mutations are associated with milder disease phenotypes and others are associated with inconclusive diagnoses for which the natural history is unknown. Finally, whereas screening for CF allows early patient identification and has expanded our understanding of early pathophysiology, there is a paucity of therapeutic studies in CF infants, and management guidelines are based on limited scientific data.

IMMUNOREACTIVE TRYPSINOGEN AND SWEAT TESTING

The first stage of all CF newborn screening programs involves measuring immunoreactive trypsinogen (IRT), a pancreatic-enzyme precursor whose concentrations are persistently elevated in the blood of

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KEY POINTS

- Newborn screening for CF algorithms vary, based on the balance between the risk of false-positive and false-negative results.
- Carrier detection, unique to algorithms with DNA mutation analysis, requires additional attention to educating affected individuals.
- CF-related metabolic syndrome includes individuals with gene mutations and intermediate (or normal) sweat chloride values.
- Anatomic and physiologic changes occur early in the lives of infants with CF.
- Care guidelines for infants with CF are based on limited scientific data and studies of therapies in infants are needed.

infants with CF [3]. The second stage involves either DNA mutation analysis (IRT/DNA) or obtaining a second IRT (IRT/IRT) and looking for persistent elevation. Whereas there is no standardized IRT detection cut-off level, using a lower cut-off improves test sensitivity and adding the mutation analysis improves positive predictive value. However, using lower cut-off levels increases the number of false-positive tests and each program must determine the balance of sensitivity and false-positive results [4]. There are two isoforms of IRT and programs vary as to which form they measure. Lindau-Shepard and Pass [5] showed that measuring both isoforms resulted in comparable performance. To further aid in reducing the number of false-positive tests, pancreatitis-associated protein (PAP) is being investigated in combination with the IRT [6]. PAP is a secretory protein which increases after sustained pancreatic stress and is elevated in neonates with CF [7]. Whereas false-positive results for both IRT and PAP have been reported in infants with renal failure [8], this approach has been proposed to avoid using DNA analysis. A second approach to decreasing false-positive results is to add mutation analysis to the IRT/IRT method [9]. This also allows a lower IRT cut-off level, improving sensitivity while reducing the number of false-positive results related to carrier detection [10▪▪]. In a recent review of CF newborn screening, Castellani and Massie [11▪] commented that 'although there is not one universal CF newborn screening protocol that will suit the heterogeneous needs of diverse regions, many options for adjusting algorithms to local conditions are now available'. Most importantly, every program needs to monitor its data regularly and conduct ongoing quality improvement to optimize patient outcomes [4,12,13].

Following detection by newborn screening, the diagnosis of CF should be confirmed by measuring sweat electrolytes, even when two disease-causing mutations are identified [14]. The sweat test, however, may be nondiagnostic due to intermediate chloride values or insufficient quantity of sweat (quantity not sufficient (QNS). The problem of intermediate chloride values may be a greater problem in programs using the IRT/DNA method since CF carriers (who naturally have slightly higher sweat chloride values) are detected [15]. Whereas the goal of screening is to identify patients with CF at the earliest age, younger and smaller patients are more likely to have QNS results [16]. Thus special attention is needed to perform accurate sweat testing so that QNS rates are at acceptable levels [17▪]. For infants with an initial QNS sweat test, a nasal potential difference can be successfully measured at select referral centers [18]. Otherwise repeat sweat testing can be done, assuring that the child is well hydrated at the time of the test. Whereas some programs have added sweat conductivity measurement to quantitative chloride measurements to help with diagnosis, conductivity has a higher rate of false-positive results [19]. Importantly, sweat test results need to be interpreted in view of the patient's genotype and phenotype to make the diagnosis of CF [20,21].

FALSE-POSITIVE SCREENING AND CARRIER DETECTION

The most common CF gene mutation worldwide is the F508del. Other mutations vary greatly between different populations, creating a need for different DNA screening algorithms [22–25]. Screen sensitivity improves by increasing the number of mutations, but this also increases the number of carriers detected (false-positive results). Studies of the emotional impact of false-positive screen results show that parents may have persisting concerns about the test's accuracy, their child's health, and the implications of having a genetic mutation [26▪]. This perception of health vulnerability persists with the parents for at least the first year, during which time infants who are CF carriers have a higher frequency of reported medical problems compared with noncarrier controls [27▪]. One way to alleviate anxiety is to shorten the time between notifying the family of a positive screen and confirming a diagnosis [28]. During this time parents often seek information from the internet or their family physician [29], and programs need to provide ongoing education to assure that healthcare providers are knowledgeable about false-positive and negative screen results [30–32].

False-positive results happen with both IRT/DNA and IRT/IRT screening algorithms; however, carrier detection is a challenge unique to programs using DNA testing. Since the initial IRT cut-off level can be lower, DNA testing decreases false-negative rates, but this must be balanced with the need to address carrier detection. Some studies suggest that one way to reduce carrier misconceptions and to improve a family's understanding is to provide structured genetic counseling at the time of the sweat test [33–35]. However, follow-up after genetic counseling with parents of carriers indicates that, whereas 94% understand their child does not have CF, only 79% understand that their child carries the CF gene and fewer than half of the parents or relatives of a carrier infant expressed any interest in personal testing [36]. Additional telephone follow-up by the program is supported by families and appears necessary to provide information and correct misconceptions about carrier status [37].

Some CF screening programs avoid the problems of carrier detection by performing two IRT measurements followed by a sweat test. This requirement for two samples (IRT/IRT) results in slight delays before the definitive diagnosis can be made (median 4.0 weeks vs. 2.3 weeks with IRT/DNA) [38]. However, the median time to diagnosis is still below the 7 weeks reported in the Wisconsin randomized, controlled newborn screening trial in which clinical benefit was demonstrated [39]. The IRT/IRT approach also has a higher risk of false-negative results due to higher initial IRT cut-off values, although there does not appear to be a significant delay in diagnosing patients with false-negative newborn screening results [40]. What is clear is the need for efficient follow-up of positive screening results and a rapid referral to a care center where not only the patient, but also the family, can have their medical and emotional needs met [41].

MILD PHENOTYPES AND INCONCLUSIVE DIAGNOSTIC RESULTS

DNA testing algorithms may include mutations which result in milder disease phenotypes or are associated with inconclusive diagnoses for which the natural history is unknown. Inclusion of these genetic variants can create confusion, the potential for misdiagnosis, and nonclear implications of the diagnosis [42,43]. For programs with little genetic variation in the population, only a limited number of mutations need to be included in the screen [44]. Expanding the panel of genetic variants in these populations will have little impact on detection rate due to the infrequency of additional mutations [42]. In other populations with greater racial and genetic variation, expanding the panel may allow other changes in the program such as negating the need for a 'failsafe' testing of particularly elevated IRT values [4,45]. However, in both situations careful consideration of which mutations to include is essential for appropriate genetic counseling and management. Of particular interest has been the inclusion of the R117H mutation. In some populations this mutation has a naturally high frequency and results in an excess number of false-positive screen results [46]. Additionally, even in combination with more typical CF mutations the impact of the R117H is altered by the intron-8 poly-T status of the patient [47].

Another consequence of expanded DNA testing is identifying infants with an inconclusive diagnosis. Specifically, these are infants with a positive newborn screen which includes one or two mutations, but physiologic measures such as the sweat test are not diagnostic of classical CF. This condition has been referred to as the cystic fibrosis-related metabolic syndrome (CRMS). Over time the sweat test may become abnormal and some of these individuals develop clinical signs of CF in later life, although the disease is generally mild [48▪▪]. Close monitoring has been proposed, although avoiding exposure to other CF patients may be important to reduce exposure to infectious agents [49].

CLINICAL OUTCOMES FROM CYSTIC FIBROSIS NEWBORN SCREENING

Improved nutrition was the primary benefit of CF newborn screening identified in the randomized, controlled trial conducted by Farrell *et al.* [39] and continues to be the most significant outcome of early detection [50]. Using additional data from this trial, Tluczek *et al.* [51] reported no difference in pulmonary function and quality-of-life outcomes between screened and control patients when controlling for pancreatic function and mucoid *Pseudomonas aeruginosa* infection. These results, however, differ from previous epidemiologic data indicating a protective benefit of newborn screening for nutritional state and pulmonary function, as well as reduced complications [52,53]. There is some evidence of improved survival in CF patients identified by newborn screening; however, this study used historical controls during a period in which there have been other significant improvements in CF care [54▪].

Even with early diagnosis and long-term preventive care in specialized CF care centers, differences exist in outcomes between programs. A comparison of US and French patients with CF detected by newborn screening demonstrated differences in

the extent of lung disease [55▪]. The screening protocols, median age at diagnosis, pancreatic function and genotypes were similar; however, the French children had a more rapid progression of lung disease based on chest radiographs when compared with CF patients in Wisconsin. This finding was further supported by the patients having significant differences in lung function (forced expiratory volume in 1 s) between 6 and 12 years of age (83 ± 19 vs. $93 \pm 18\%$ predicted at age 12 for France and Wisconsin, respectively). These differences partially disappeared when patient weight or hospitalization data was added to the estimating model, suggesting there might be other risk factors for deterioration associated with region. The authors did not identify any specific risk factors, but suggested that nutrition, environment, or the healthcare delivery system might be contributing.

One unexpected potential consequence of newborn screening is the potential increased cost of caring for young children with CF. Between 2001 and 2007 the annual cost of treating a child below 11 years of age with CF increased nearly 10-fold based on private insurance payments [56]. Whereas these increased costs were not the result of newborn screening, the earlier age at diagnosis and recommendations for close monitoring of all infants with CF predict that the overall cost for care will continue to increase [57,58▪].

An additional outcome of newborn screening may be a decreasing prevalence of CF due to at-risk couples obtaining prenatal testing [59▪]. Early detection of an infant with CF provides the opportunity to identify adult relatives at risk for having a child with CF, but, interestingly, nonparent adult relatives, particularly males, do not commonly pursue testing [60].

EARLY PATHOPHYSIOLOGY

Newborn screening and early identification provide the ability to evaluate CF patients before they develop clinical disease. Chest computed tomography (CT) scanning has the strongest association with later development of lung disease in patients with CF [61]. Limited CT scans have a lower ionizing radiation dose and quantitative anatomic changes associate with future lung disease, plus these anatomic changes correlate with early airway inflammation [62]. Lung function can be measured by a variety of techniques, including the lung clearance index (LCI), which measures distribution of ventilation and detects early differences between infants with CF and healthy controls [63]. Chest CT and LCI are only weakly associated in infants with CF, suggesting that early anatomic changes precede functional changes [64].

Infection and airway inflammation have been identified in asymptomatic infants with CF [65]. Airway inflammation is associated with eventual lower lung function, and airway infection is associated with a greater decline in lung function over time [66▪▪]. Additionally, airway inflammation is associated with the nutritional status of infants and young children with CF [67▪]. Surveillance bronchoscopy demonstrates bacterial infection in 27%, neutrophilic inflammation in 67% and reflux in 42% of infants with CF during the first 6 months of life [68]. However, in a well controlled clinical trial of routinely scheduled bronchoscopy, Wainwright *et al.* [69▪▪] showed no difference between patients managed with and without routine bronchoscopy.

Infants detected by CF newborn screening develop early infection with *Staphylococcus aureus* followed often by *P. aeruginosa* [70]. Bacterial acquisition does not seem to be affected by cohorting patients into *P. aeruginosa*-positive and negative clinics [71▪], although previous studies have indicated a higher risk of infection when infants are seen in the same location as older patients [72]. Early *P. aeruginosa* detection may be aided by the use of antibody testing, although several tests exist and the optimal antibody is still not defined [73].

Finally, whereas the earliest identified benefit of NBS for CF is improved nutrition, even with screening, infants have less than normal growth [39]. Low levels of insulin-like growth factor 1, first identified in the pig model of CF and confirmed in infants identified by newborn screening, may partially account for this finding [74▪].

THERAPY

There are almost no studies of specific therapies in infants with CF. Whereas guidelines have been developed to recommend management, these are based mainly on expert recommendations and not evidence-based results [57,58▪,75].

Jadin *et al.* [76▪] recently noted that infants fed exclusively breast milk during the first 2 months of life, compared with exclusively formula-fed infants, appear to have a long-term respiratory benefit with fewer positive cultures for *P. aeruginosa*. However, infants who were exclusively breast fed for the first 6 months of life had less growth compared with formula-fed infants. Interestingly, mothers of CF infants are less likely to breastfeed than mothers of non-CF infants [77]. In addition to possible benefits for respiratory health, breast feeding may improve the quality of the mother–child

relationship and should be encouraged by newborn screening programs, even though growth may be slightly less. In addition, all infants with CF should receive supplemental vitamins, since vitamin deficiency is one morbidity which can be potentially prevented with newborn screening [78].

No recent controlled studies of any respiratory treatment have been published and the only controlled trial of antibiotic therapy in infants identified by newborn screening suggested that preventive antibiotics had only limited value [79]. At this point there is a profound need for clinical studies of therapies in infants with CF. Recently Accurso *et al.* [80] reported effective, targeted therapy for CF patients with cystic fibrosis transmembrane conductance regulator gating mutations. Targeted therapies for other mutation classes are currently underway, and studies of extending therapy to infants with gating mutations are being started. Therapy targeted at the basic defect holds great promise, especially when initiated in the newborn before the onset of significant lung disease [81].

CONCLUSION

Newborn screening for CF has come a long way since the first CDC workshop in 1997 recommended further study [82]. Based on modern criteria, CF clearly should be included in newborn screening programs [83]. Screening for CF has created some new challenges, particularly related to DNA testing, carrier detection, and inconclusive diagnoses. But excellent resources are available to assist program development [10▪▪]. Even with these new challenges, the future for the CF patient is improving as new therapies directed at the primary genetic and biochemical abnormalities become available [84].

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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