Newborn screening for cystic fibrosis
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Early diagnosis of cystic fibrosis (CF) provides an opportunity to improve disease control and prevent early complications. Of patients with CF in the United States, 10% are identified early through newborn screening (including infants born in Colorado, Massachusetts, New Jersey, New York, Wisconsin, Wyoming, and parts of California, Connecticut, Pennsylvania, and Montana). Successful screening programs in these states have stimulated other states to consider adding CF screening to their newborn programs. Additionally, new technology permits expanded screening for numerous genetic conditions. Genetic screening, such as that used most frequently for CF, creates new challenges for the clinician, including atypical disease presentations and carrier detection. In this review, we examine the many advances in CF newborn screening and early care that were reported during the last few years. Curr Opin Pediatr 2003, 15:309–315 © 2003 Lippincott Williams & Wilkins.

Cystic fibrosis (CF) is diagnosed once in every 4000 live births in the United States, making it six times more common than phenylketonuria and equal in incidence to congenital hypothyroidism (2001 Colorado State Health Department data). Recent technologic advances permit almost unlimited expansion of newborn screening programs, while creating new challenges related to genetic screening and detection of conditions, such as CF, that do not have definitive therapies [1•,2,3]. Newborn screening programs for CF have existed in many countries for nearly 40 years, although debate continues whether these programs should be widespread in North America [4•,5,6]. Following the publication of encouraging outcomes from two large randomized, controlled trials of CF newborn screening, an increasing number of states are beginning to include CF in their public health screening armamentarium [7••,8•]. During the last few years numerous investigators have reported on the benefits related to earlier diagnosis of CF [6,9–11,12•,13–15,16•,17,18]. Additionally, new therapies for CF have been developed to manage many of the complications [19•,20,21•]. These therapies, as well as future new therapies, are likely to have their greatest impact on clinical outcome when early detection is possible. Newborn screening offers the best chance for successful early detection.

Newborn screening for CF, similar to every major medical advance, has generated new challenges (Table 1). Most CF newborn screening programs incorporate genetic screening (ie, testing for specific DNA mutations) [22]. Because the CF gene has many different potential mutations, determining for which mutations to test is important to assure optimal testing sensitivity [23••]. Certain mutations can be related to less severe or atypical disease, adding complexity to the choice of specific mutations to screen [24,25]. Genetic screening for an autosomal recessive disease also means that asymptomatic carriers, or heterozygotes, are often identified [26••]. Thus, although early detection is valuable for the individual patient, genetic detection raises new challenges for the healthcare system [27••]. Future additions to newborn screening programs will likely involve genetic detection, so the experience with CF screening is extremely important [28,29].

Screening rationale
Newborn screening is a program aimed at the early identification of medical conditions for which early interventions can lead to the elimination or reduction of associ-
ated mortality, morbidity, and disability [30••]. CF typically presents during the first year of life with failure to thrive related to fat malabsorption and lower respiratory tract infections from specific bacterial pathogens. Although the median age at diagnosis is 6 months, the mean age at diagnosis is 3.1 years, indicating that a significant percent of patients have the diagnosis delayed for many years [31]. Diagnosis usually occurs after a patient has experienced multiple complications related to CF, unless it is diagnosed by newborn screening or because the patient is tested due to a positive family history. Recently, an increasing number of diagnoses have been made prenatally, either because of echogenic bowel detected by prenatal ultrasound [32], or by amniocentesis and genetic testing in pregnancies at risk for CF.

Mortality is rare in infants with CF during the first year of life. Early mortality is usually related to meconium ileus; however, in one large controlled study of CF newborn screening, the only deaths unrelated to meconium ileus occurred in the conventionally diagnosed group [8•]. Also, serious complications can occur during the first year of life in infants with undiagnosed CF. (Table 2) Life-threatening complications include severe protein-calorie malnutrition (kwashiorkor), hemolytic anemia, and intracranial hemorrhage caused by vitamin K deficiency [33–35,36•]. Although not life-threatening, even mild malnutrition during the first few years of life can affect long-term growth and may affect lung development and later lung function [37]. This malnutrition, as well as failure to recognize early respiratory tract problems, contributes to most infants with CF having abnormal lung function at the time of conventional diagnosis [38••]. Newborn screening avoids this complication and results in superior growth, continuing until at least 13 years of age [39••].

Newborn screening and early detection provide additional benefit to patients with CF with complex medical problems [40]. Holmgren et al. reported three children with bronchopulmonary dysplasia who had prolonged oxygen supplementation and poor weight gain [41]. Because of the existing chronic lung disease, the diagnosis of CF was significantly delayed. Earlier diagnosis would have led to pancreatic enzyme and salt supplementation, probably reducing the degree of failure to thrive and preventing the metabolic alkalosis seen in two of these patients.

Finally, newborn screening and early diagnosis of CF provide a unique opportunity to study, as well as treat, children before the development of airway infection, inflammation, and permanent damage. Investigators are beginning to answer the question of how the abnormal cystic fibrosis transmembrane regulator (CFTR) protein results in the medical problems encountered by the clinician [42]. Infants detected of having CF by newborn screening provide one of the only opportunities to study the pathophysiology of the disease before complications.

### Cystic fibrosis screening techniques

Several approaches exist to screen newborns for CF. In 1964, Wiser and Beier suggested measuring albumin in meconium as a screening test for infants [43]. The technique, however, does not lend itself well to statewide screening and lacks sensitivity. In 1979, Crossley et al. reported the use of the dried blood spot to detect immunoreactive trypsin (IRT) as a screen [44]. Initial studies showed that this marker rapidly declined after birth in healthy infants. A two-sample program, where the first blood was drawn by day 3 and a second sample was obtained at 2 weeks or later in initially positive patients, was 95.2% sensitive and 32% to 74% specific, depending on the IRT values used for recall [45••]. This approach, however, requires two blood samples and following the identification of the CF gene in 1989, a two-tier IRT/DNA strategy became possible [46,47]. With this approach, a highly sensitive, but relatively nonspecific point is chosen to define an elevated IRT. Then, samples with an elevated IRT are further tested for one or several CF genetic variants [48]. Although many programs initially screened only for the most common CF mutation (ΔF508), generally a panel of gene mutations should be used, based on the local prevalence of different mutations [23••]. This approach has similar sensitivity to the double-IRT approach, but avoids the need for a second sample. One drawback of the IRT/DNA technique is that it will detect heterozygous individuals who do not have CF but only carry the gene. To further complicate this approach, CF heterozygotes tend to have higher IRTs than the general population, resulting in an increased number of detected carriers who will require genetic counseling [49•,50]. With either screening technique, subjects identified to have the CF mutation...
should have the diagnosis confirmed by standardized sweat electrolyte testing [50–54]. Additionally, because both techniques begin with testing for IRT, they both can be falsely negative in children with meconium ileus at birth [55,56]. Because the diagnosis of meconium ileus mandates further evaluation for CF, this false negative screening result should never lead to a missed diagnosis.

**Challenges arising from cystic fibrosis screening**

Screening based on DNA has created several challenges that are different from traditional newborn screening. Although CF is a single gene defect, numerous potential mutations exist in the gene. The frequency of specific mutations vary worldwide so that every DNA screening program needs to consider the most common mutations in the region to develop the ideal screening panel [57,58]. Thus, whereas one program might only screen for a few specific mutations, in an area with greater genetic variation, the screen might involve several dozen mutations [59].

Probably the greatest challenge for a DNA-based newborn screening program is how to manage genetic counseling [27•,60]. Heterozygote detection occurs with DNA-based testing and creates a special demand for genetic counseling. If a single CF gene mutation is identified, then patients should be referred for a sweat test to rule out disease. Most commonly, the sweat test will be normal, indicating the patient is most likely a heterozygote without risk for CF. The infant, however, does have the risk of passing on the gene when he/she later has children, and the infant’s parents are identified as having at least one gene for CF. Additionally, the infant and heterozygote parent may or may not be at risk for other, CFTR-related medical problems [24,61•]. Recent studies have shown that heterozygote “carriers” of the CF gene may be at increased risk for pancreatitis, allergic bronchopulmonary aspergillosis, other chronic lung diseases, and infection from atypical mycobacteria [62–65]. This raises the need to discuss medical and genetic risks with the parents, plus potential further screening to look for yet undisclosed CF genes. The risk of undisclosed CF genes is significant and may be as high as 6% [26•].

Infrequently, a single gene is identified and the sweat test is indeterminate (ie, the patient may have an atypical form of CF with a sweat chloride of 40 to 60 mEq/L). Patients with one gene and borderline or “normal” sweat electrolytes are particularly difficult to assess, because the clinician can neither assure the parents that the child does or does not have CF [66]. New specialized tests (eg, measuring nasal electrical potential difference) may eventually aid in diagnosing patients with indeterminate disease [67,68]. Currently, any patient with a borderline sweat test should be evaluated with an expanded genotype, including not only a large panel of CF mutations, but also examination for potential polymorphisms or modifiers (eg, the 5-polythymidine allele) [69,70]. Additionally, complete sequencing of the gene may be necessary to look for less frequent mutations [71,72]. This can be particularly important in different racial groups with different genetic variations [73,74]. Associated conditions that should be monitored include airway colonization with typical CF-related bacterial pathogens, nutritional deficiencies (eg, hypoalbuminemia and fat soluble vitamin deficiencies), fat malabsorption, hypo-electrolytemia, sinusitis, and pancreatitis.

As with many genetic conditions, CF phenotypes vary greatly from individual to individual [75]. Patients with mild disease, with pancreatic sufficiency and minimal lung disease, often have delayed conventional diagnosis [76]. These patients generally have a better long-term prognosis than patients who are symptomatic during the first couple years of life. Early detection by newborn screening may not be a benefit for these few patients. One concern is whether early detection could increase the risk of certain bacterial infections by exposing infants to other patients with CF at an earlier age than would occur with conventional diagnosis. Farrell et al. noted that *Pseudomonas aeruginosa* detection was greater in one CF center, where infants were cared for in the same clinic compared with a second center with a special newborn clinic [77]. These findings suggest that CF center care might put a child at risk for acquiring bacterial pathogens. Subsequent studies with larger populations, however, suggest that this risk is not related to age at diagnosis [78]. Additionally, recent infectious disease guidelines developed by the US CF foundation address techniques to avoid patient-to-patient spread of bacteria.

Finally, genetic testing may have an impact on future reproductive planning. [79•,80,81•]. The potential for impacting family planning has led the American College of Obstetrics and Gynecology to suggest that all pregnant women be offered prenatal genetic testing for CF [82•,83•]. In a study of 4879 women who partook of prenatal testing, 124 were heterozygotes [84]. When 106 partners were tested, 5 couples were identified as having a 25% risk of having a pregnancy with CF. This stimulated four to have prenatal testing. Prenatal CF screening has also been proposed in other countries [85]. How universal prenatal screening would have an impact on the needs for genetic counselors and prenatal testing can only be speculated. [84,86,87]. Likely, this issue will increase as genetic causes for other diseases are identified.

**Therapy for early disease**

One of the most important benefits of newborn screening and early diagnosis of CF is the ability to treat patients before serious complications occur. Nutritional abnormalities in patients CF are common during the first year of life [88•]. Abman et al. showed that hypoalbu-
minemia could occur by 3 weeks of age, and that low albumin related to an increased chance for serious respiratory infection [89•]. Early use of pancreatic enzymes will prevent hypoalbuminemia. Early diagnosis by newborn screening, however, does not completely avoid the potential for malnutrition in children with CF [90,91]. Although only 59% of infants with CF are enzyme deficient at 2 months of age, 92% will require supplemental enzymes by the time they are a year old [92•]. Previously, malabsorption was diagnosed by a 72-hour stool fat collection, or inferred by poor weight gain. Poor weight gain, however, can be a late finding of malabsorption [93•]. A recently developed test for stool elastase can assist with diagnosing pancreatic deficiency. This non-invasive test has a 92% diagnostic accuracy for detecting pancreatic maldigestion and is superior to the acid starch orat, which is used to diagnose steatorrhea [94,95].

Related to fat malabsorption, essential fatty acid, vitamin, and mineral levels may be low in infants with CF [96,97]. Although pancreatic enzyme supplements will reduce the problem of fat-soluble vitamin absorption, supplements with vitamins A, D, E, and K are advisable to avoid deficiency [98,99]. Another preventable nutritional complication is hypochloremia and dehydration related to excess salt loss through sweating. Early detection allows for salt supplementation in the first year of life. Liver function should also be monitored because cholestasis is common. Ursodeoxycholic acid is effective in treating cholestasis if detected early [100]. Most importantly, early detection by newborn screening combined with treatment in a CF care center results in nutritional improvements that persist for more than a decade when compared with infants who are conventionally diagnosed [7].

Lung disease related to CF is produced by a combination of infection and inflammation. Neutrophil-dominated inflammation results in an excessive release of elastase and reactive oxidants that stress the body’s natural defenses [101]. These injurious chemicals can produce airway damage and the bronchiectasis typically seen in patients with CF. Bacterial pathogens and neutrophils are present in the airways of most patients with CF studied at 1, 2, and 3 years of age [102••,103]. The density and prevalence of these bacteria increases progressively during these years. This increasing bacterial presence correlates with increasing respiratory symptoms and worsening oxygen saturation. To reduce the quantity of bacteria, prophylactic antibiotics have been studied [104]. This approach was successful in one study of patients with CF diagnosed by newborn screening, although concern was raised for increasing the risk of P. aeruginosa colonization [105]. P. aeruginosa is present in over a third of patients by 2 or 3 years of age, and infection accelerates the development of lung disease in CF, contributing to increased mortality and hospitalization by 7 years of age [106•,107,108]. Inhaled tobramycin is currently being studied in these young children. Studies in older children suggest that P. aeruginosa can be eradicated if treated early [109•].

Neutrophil-dominated inflammation increases with increasing bacteria density, although even in the absence of positive cultures, both neutrophils and proinflammatory cytokines may be increased in the airways of infants with CF [102••]. Whether treatment directed toward reducing inflammation can reduce airway damage is still not clear [110]. However, airway damage is more likely in the presence of antioxidant nutritional deficiencies (eg, vitamin E) plus excess oxygen free radicals caused by inflammation. Studies are yet to be conducted that will answer the question if airway damage can be modified by antioxidant or antielastase therapy.

Early treatment requires early detection, as is provided with newborn screening, and close monitoring. Bacterial colonization is usually followed with frequent upper airway cultures [111]. Recent developments in infant pulmonary function testing allow for respiratory monitoring in infants similar to monitoring in older patients [112•,113]. Additionally, care in specialized CF care centers provides expertise in nutritional and psychological support. This close monitoring and early intervention result in an overall improved outcome for patients with CF [16•].

Summary
Life expectancy for patients with CF has been increasing steadily since the original description of the condition in the late 1930s. Many of the advances in care include close monitoring and early intervention for malnutrition and respiratory infection [114,115••]. Newborn screening provides the opportunity to initiate monitoring and treatments at the earliest possible point, with little risk [5]. Care, however, needs to be well organized and care providers need to be well educated about the significance of a positive or negative screen. Importantly, screening for a condition never “rules out” the condition, but only reduces the likelihood a patient has the diagnosis [116]. Confirmatory testing should be obtained for both screen-positive and, if clinically indicated, for screen-negative patients. Finally, because screening often identifies the patient in a preclinical state, the clinician needs to be particularly vigilant in monitoring the patient and educating the family on early signs of pathology.

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