

Cystic Fibrosis: Refining the Approach to Newborn Screening

Newborns have been screened for cystic fibrosis (CF) in Colorado since 1982; 20 years later, only 10% of newborns in the United States were being screened. Now the tide has turned, and screening is done in all states except 3, where it is still in the planning stage. "All screening programs aim at maximizing the diagnosis of cystic fibrosis and minimizing...unnecessary sweat tests, detection of unaffected carriers and the recognition of infants with equivocal diagnoses."¹ In this issue of *The Journal*, Sontag et al report on a proposed new protocol for screening, with retrospective Colorado data, that achieves those aims.²

Screening for CF was being discussed in the 1960s and 1970s, but measurement of meconium albumin, the only test available for mass screening, performed poorly for both sensitivity and specificity. In 1979, screening became a true possibility with the seminal discovery in New Zealand that immunoreactive trypsin (IRT) levels were elevated in babies with CF (although later becoming much lower than normal in most) and could be measured in the dried blood spots already being collected for other screening tests, then principally phenylketonuria and hypothyroidism.³ Screening programs for CF were started on a limited scale in the United Kingdom, Europe, Australia, and New Zealand. Colorado and a few other states were not far behind. With screening came growing evidence of clinical benefit obtained from 2 randomized controlled trials and several observational cohort studies. Clinical advantages in patients who were screened, including better growth and other nutritional indicators, less morbidity, less early mortality, and improved lung function, have been recently reviewed.^{4,5}

It is now clear that babies should be screened for CF,⁶ but how the screening tests should be conducted remains the subject of debate. Measurement of IRT in dried blood spots has good sensitivity in the first few days, but poor specificity, with a positive predictive value of only 3% to 10%.⁷ Early programs therefore adopted a 2-stage test; an elevation of IRT level on the initial sample led to a repeat test at approximately 2 to 4 weeks, when the positive predictive value was approximately 50%. With the identification of the CF transmembrane conductance regulator (CFTR) gene in 1989 and the discovery of a prevalent mutation, p.F508del, it was possible to complete screening with a single sample, conducting a DNA test on the original sample when the IRT level was higher than a predetermined cutoff level. Finding at least 1 significant mutation led to a sweat test, still the definitive confirmation for all testing protocols. Today, multiple mutations can be tested. However, there are >1000 CFTR mutations known, many of them private (confined to 1 family) and

many harmless polymorphisms and mild mutations not leading to known clinical harm, so complete CFTR screening with mutation analysis is not a reality. We recently reviewed the many algorithms for screening that have arisen,⁷ which include conducting a sweat test as soon as an elevated IRT level

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is found, testing for IRT level in a second sample (IRT/IRT), selecting first samples with elevated IRT levels for DNA analysis for the common mutation or a variable number of others, depending on the population background (IRT/DNA), and combining aspects of these methods. There are pros and cons for all these approaches, including different specificity, sensitivity, and costs, and most important, the identification of CF carriers in any algorithm that includes DNA analysis. Carrier identification is usually regarded as undesirable, leading to much anxiety for parents and for the clinicians who must counsel them.

In the United States, requesting a second newborn screening blood sample from all babies is required in 9 of 50 states and carried out in a few others. The Colorado program has taken advantage of this. On the basis of >25 years of experience in CF screening, workers have devised a new screening algorithm that was thought likely to improve sensitivity compared with an IRT/IRT approach and also decrease the carrier detection inherent in an IRT/DNA algorithm. They were then able to test their new algorithm by using retrospective data from the program. The impressive results show far fewer second IRT tests, fewer mutation analyses needed, fewer carriers detected, fewer sweat tests, increased sensitivity, and much reduced costs—just what the doctor ordered! This depends on the ability to link first and second samples with a new laboratory information system, so that the second sample only has an IRT test when the first result is elevated, and the use of a fail-safe approach when both IRT results are high but no mutation is found. In addition, it depends on the routine collection of a second newborn screening sample—something not uncommon in the United States, but uncommon elsewhere.

Therefore, this raises the question of routine second sample collections mainly thought to be justified in relation to screening for congenital hypothyroidism, in which there may be a normal level of thyroxine and a delay in the elevation of thyrotropin in well-compensated but permanent hypothyroidism, and in screening for congenital adrenal hyperplasia. Collecting and testing second samples is a significant expense, and there is no consensus that it is fully justified. The American Academy of Pediatrics guidelines for hypothyroidism screening published in 2006 do not specifically recommend routine second screens because of: "1) increased cost, 2) relatively low yield of cases, 3) diversion and dilution of key personnel, 4) inability to implement

CF	Cystic Fibrosis
CFTR	CF transmembrane conductance regulator
IRT	Immunoreactive trypsin

new programs, and 5) absence of such cases missed in primary TSH screening programs...⁸ A study to determine the value of routine second specimen testing is underway, sponsored by the US Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. (H. Hannon, Centers for Disease Control, personal communication). In the meantime, if routine second screening does not become more widespread, it will not be possible for the Colorado algorithm for CF screening to be taken up widely, although it should probably be adopted by all states that currently collect a second sample. The method of looking at new approaches by carefully dissecting retrospective data is to be commended, and this approach has wide applicability to all screening programs. ■

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Automated Adjustment of Oxygen in Ventilated Preterm Infants: Turn on, Tune in, ROP out?

The death of newborns from respiratory failure has been recognized and noted to occur more frequently in preterm infants for >2000 years.¹ In the mid 20th century, the term respiratory distress syndrome (RDS) was coined to describe the often lethal respiratory distress and episodic apnoea, cyanosis, and bradycardia seen in preterm newborns, which began at or shortly after birth and progressed over 72 hours. Hyaline membrane disease (HMD) described the striking pathological features seen on post-mortem examination of lung tissue of infants who died.

Illustrating doctors' enduring enthusiasm for introducing new and unproven therapies, oxygen was first given to newborns in 1780, within 6 years of its discovery.¹ Oxygen supplementation for newborns began in earnest in the 1940s. Although oxygen given in high concentrations likely improved survival from RDS, it resulted in an epidemic of blindness caused by retinopathy of prematurity, thereby starting modern-day neonatologists' ambivalent affair with oxygen.² In an attempt to prevent blindness, oxygen use was curtailed, which led to an increase in deaths from HMD and was associated with a rise in the frequency of spas-

tic diplegia.² Therapy for RDS has progressed markedly in the last 60 years. The introduction of mechanical ventilation was met initially with limited success initially and, with the emergence of bronchopulmonary dysplasia, which was attributed partly to excessive oxygen exposure.³ Continuous positive airways pressure showed an impressive reduction in mortality in a small case series of infants with established severe RDS.⁴ Antenatal steroids were demonstrated to reduce the frequency of RDS and death in preterm infants.⁵ Techniques of mechanical ventilation, which included the use of positive end-expiratory pressure, were refined, and exogenous surfactant therapy followed, resulting in immature infants surviving in greater numbers.⁶ These survivors, however, had substantial rates of chronic lung disease (CLD) and neurological dysfunction. Vitamin A supplementation⁷ and caffeine therapy⁸ were subsequently demonstrated (modestly and substantially, respectively) to reduce the rate of chronic lung disease. Despite showing promise in cohort studies, use of nasal continuous positive airways pressure in preference to endotracheal ventilation from birth did not reduce the rate of CLD in a recently reported randomized trial.⁹

Although the fraction of inspired oxygen (FiO₂) given to infants with respiratory distress was once determined with clinical assessment of color, in time this was aided and

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CLD	Chronic lung disease
FiO ₂	Fraction of inspired oxygen
HMD	Hyaline membrane disease
RDS	Respiratory distress syndrome
SpO ₂	Oxygen saturation