Challenges in Cystic Fibrosis Newborn Screening and Recommendations for Primary Care Physicians

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During the past decade, newborn screening (NBS) for cystic fibrosis (CF) has disseminated worldwide after endorsements by the Centers for Disease Control and Prevention and the CF Foundation. Similar to widespread introduction of other NBS programs, CF NBS implementation occurred on a region-by-region basis by using a wide variety of screening strategies and analytical methods. All strategies begin with measurement of the biomarker, immunoreactive trypsinogen, and should end with a sweat chloride test. Although these protocol variations have differing screening efficiency or effectiveness, all CF NBS programs have provided a better opportunity for healthier outcomes than traditional strategies that rely on signs/symptoms for triggering the diagnostic processes associated with delays and discrimination.

In an ambitious effort to optimize CF NBS for their region’s diverse population, California analyzed and planned their strategy over 2 years, leading to specific goals. In essence, California organized a strategy that applied cystic fibrosis transmembrane conductance regulator gene (CFTR) sequencing for the first time, required detection of 2 mutations for designation of positive screening, and recommendation of a sweat chloride test. This NBS method relies heavily on the interpretation of CFTR variants, as not every CFTR genetic change will result in CF.

RECENT ADVANCES IN CFTR GENETICS

CF began as, and remains, a clinical diagnosis. The recognition of the Mendelian inheritance of a well-characterized phenotype allowed the detection of the gene responsible for CF, and of common mutations. These mutations (mostly European derived) were the basis for early CF genetic tests used for diagnosis and screening. However, as recognition of CF widened, and knowledge of the CF phenotype expanded to include milder and atypical phenotypes, testing for just the common mutations proved inadequate. Carrier screening and NBS both rely on interpretation of the disease liability of a CFTR variant in the absence of phenotype. This change from identifying a genotype in individuals with known disease, to the use of genotype to predict phenotype is a common challenge in the advent of personalized medicine. Testing for more variants, without knowledge of the consequences of those variants, leaves clinicians and patients in uncertain territory.

To address the more than 2000 variants identified in CFTR, the US CF Foundation has assembled an international consensus group to supervise annotation in CFTR. The Clinical and Functional Translation of CFTR (CFTR2) project has used clinical characteristics, functional testing, and population/penetrance analysis to assign a disease liability “call” to CFTR variants. The mutation calls are being updated, with most current information available on the user friendly CFTR2 Web site (www.cftr2.org), as illustrated in Fig 1A. The Web site contains information for general and scientific users on the call of a
variant as well as clinical and functional phenotype severity (Fig 1 B–D); however, the CFTR2 project does not allow comprehensive prediction for 2 reasons. First, to date only 276 variants have been analyzed. This represents most alleles seen in patients with CF, but the large number of untested remaining variants may contain variants more common in non-Europeans. Second, certain annotated mutations may cause CF in some individuals or may result in no phenotype. In the study by Kharazzi et al, both occurrences resulted in newborns with a CFTR-related metabolic syndrome (CRMS) diagnosis.
The development of mutation-specific therapies has led to great advances in the understanding of CFTR genetics and molecular pathology. Variations in the CFTR sequence can result in absence or dysfunction of the protein. This can occur in several different patterns that allow mutations to be characterized according to functional classes or according to therapeutics that may correct the defect.

**DESIGN AND DISCOVERIES OF THE CALIFORNIA CF NBS PROGRAM**

The large number of screened newborns and the ethnic diversity of the population are strengths of the California study, as well as the excellent surveillance component. There have been many valuable discoveries from the 5 years of their data analyses, including identification of novel CFTR variants with disease liability and the overall influence of gene sequencing, including its contribution to relatively high positive predictive value, and the impact of their multistep system on diagnostic outcomes. Additionally, in the era of mutation-specific therapies, an NBS protocol that identifies patients with CFTR mutations amenable to specific therapies at the time of diagnosis will allow early treatment and perhaps further the NBS goal to prevent the sequelae of disease.

One of the most impressive features of the California program was a design addressing 6 goals that seemed attractive at the time. The goal to focus on “severe CF” is difficult to translate to a screening program, as CF is a heterogeneous disease in which severity cannot be predicted from birth, especially because early diagnosis through NBS allows prevention of malnutrition and is associated with less lung disease. The California NBS protocol led to increased diagnosis of CRMS, which is not a severe condition and may be only a transient diagnosis. Of those cases that might have been “discharged” in other screening protocols, the benefit of a CRMS diagnosis with uncertain prognosis (increased surveillance and recognition of CFTR-related disease) compared with the potential harm (unnecessary increased testing and possible psychological impact) is unknown.

There are other limitations/shortcomings in the California program and also some disconcerting, if not alarming, outcomes. For instance, the median age of referral was 34 days, that is, beyond the neonatal period. Thus, one can argue that the goal to “report newborn screening results efficiently” was either not met or that the CF centers did not provide efficient follow-up evaluations. There was also a surprising paucity (12.1%) of genetic counseling delivered, although it was “offered” routinely. Such limited uptake is a particular concern when there are future reproductive implications for families. Finally, the sensitivity of the multistep algorithm at 92% is less than ideal, and the identification of 4 deaths that were “likely CF related” is alarming, especially in view of the very low mortality of CF after early diagnosis.

**CONCLUSIONS AND RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS**

We conclude that the unique California NBS method for CF has contributed significantly to our understanding of CF and the impact
of NBS with CFTR sequencing. This strategy yields the highest positive predictive value ever observed in CF NBS and allowed California to meet their goal to “minimize the burden of false positives....” On the other hand, the diagnostic outcomes are less desirable than seen with other algorithms because more CRMS than CF cases were detected, creating an unmeasured “burden” for families and CF centers. Ultimately, it is important to keep in mind that CF remains a clinical diagnosis and that no public health algorithm for CF NBS and no Web site such as CFTR2 can replace clinical acumen. Because of unevaluated or variably penetrant CFTR variants, even a Mendelian disease such as CF has a limit to genetic determinism. In addition, the 1.2% mortality rate reported emphasizes the crucial importance of striving for the highest sensitivity possible and the need for vigilance by primary care physicians, who irrespective of the screening test results for any disorder on the NBS panel need to be alert for “missed cases.” Finally, because parents of NBS-positive infants are accessing CFTR2 before follow-up, we also recommend that primary care physicians become familiar with the physician components of CFTR2 and also the CF Foundation’s NBS Web site (https://www.cff.org/What-is-CF/Testing/Newborn-Screening-for-CF/).

**ABBREVIATIONS**

CF: cystic fibrosis  
CFTR: cystic fibrosis transmembrane conductance regulator gene  
CFTR2: Clinical and Functional Translation of CFTR  
CRMS: CFTR-related metabolic syndrome  
NBS: newborn screening

**REFERENCES**

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