15. Feldstein AE, Alkhouri N, De Vito R, Alisi A, Lopez R, Nobili V. Serum cytokeratin-18 fragment levels are useful biomarkers for nonalcoholic steatohepatitis in children. Am J Gastroenterol 2013; 108:1526-31.

16. Alkhouri N, Sedki E, Alisi A, Lopez R, Pinzani M, Feldstein AE, et al. Combined paediatric NAFLD fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. Liver Int 2013;33:79-85.

New Challenges in the Diagnosis and Management of Cystic Fibrosis

New challenges have arisen in the diagnosis and clinical management of children with cystic fibrosis (CF), especially during the past few years, when novel-but-confusing terminology has been introduced. We will briefly explain the origin of and hopefully clarify the new terms, including CF transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS), CFTR-related disease (CFTR-RD), CF Screen Positive, Inconclusive Diagnosis (CFSPID), and delayed CF. Traditionally, CF has relied on the clinical recognition of characteristic signs and symptoms, but newborn screening (NBS) has truly been a "game changer," leading to routine diagnosis of asymptomatic children. CF is an autosomal-recessive disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene that encodes a cyclic adenosine monophosphate–regulated chloride and bicarbonate channel expressed at the apical membrane of epithelial cells. It is the most common life-threatening monogenic condition in the white population with an estimated birth prevalence of 1 in 1500-4000 newborns in European countries and European-derived populations, such as Americans, and eventually causes characteristic signs/symptoms.[1]

See related article, p 1469

According to consensus guidelines developed by the Cystic Fibrosis Foundation and published in *The Journal* in 2008, individuals identified by NBS can be diagnosed with CF by a sweat chloride value ≥60 mmol/L or a level of 30-59 mmol/L if they have 2 disease-causing mutations in the *CFTR* gene.[1] During the process of developing these guidelines, it was recognized that NBS introduced a new complexity and diagnostic dilemma, namely infants with abnormal screening tests as the result of elevated immunoreactive trypsinogen (IRT) levels but inconclusive sweat tests and/or DNA results.

Thus, a new disorder, although not necessarily a disease, was literally invented during another consensus conference published subsequently in *The Journal* in an article that created the label CRMS for CFTR-related metabolic syndrome.[2] In general, CRMS is used to describe infants with elevated levels of IRT but inconclusive sweat and DNA test results. CRMS should be used for an infant who is asymptomatic and hypertrypsinogenemic with either a sweat chloride concentration of 30-59 mmol/L if age <6 months or 40-59 mmol/L if age ≥6 months, on at least 2 occasions, and completed expanded genetic analysis with fewer than 2 CF disease–causing mutations or a sweat chloride concentration <30 mmol/L if age <6 months, or <40 mmol/L if age ≥ 6 months, and 2 *CFTR* mutations, in trans, of which no more than one is known to be CF disease–causing. Although this condition is clearly not a metabolic disorder, the designation metabolic syndrome was established in part to have a medical code for billing purposes under the *International Classification of Diseases* system, namely 277.9. However, CRMS has not been accepted in Europe, where another term,[3] CFSPID recently was proposed to describe infants with a normal sweat chloride (<30 mmol/L) and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences or an infant with an intermediate sweat chloride (30-59 mmol/L) and one or no *CFTR* mutations.

In addition, still another designation has been established for CFTR-RD to describe symptomatic individuals beyond infancy who have sweat chloride values <60 mmol/L and up to 2 *CFTR* mutations, at least one of which is not clearly categorized as a CF-causing mutation.[4,5] Thus, CFTR-RD is a clinical entity associated with CFTR dysfunction that does not fulfill diagnostic criteria for CF but is accompanied by signs/symptoms that may include congenital bilateral absence of vas deferens, acute recurrent or chronic pancreatitis, or disseminated bronchiectasis. Finally, Groves et al[6] have introduced in this issue of *The Journal* another term, delayed CF, to describe patients eventually diagnosed with CF after initially intermediate sweat chloride values, whose condition evolves over time to meet the criteria for a definitive diagnosis. This situation should be distinguished from patients with CF who are

CF	Cystic fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFSPID	Cystic Fibrosis Screen Positive, Inconclusive Diagnosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-RD	Cystic fibrosis transmembrane conductance regulator–related disease
CRMS	CFTR-related metabolic syndrome
IRT	Immunoreactive trypsinogen
NBS	Newborn screening

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diagnosed after the neonatal period as the result of either false-negative NBS tests or another cause of failed screening that leads to a missed case.

With such a complex family of CFTR-associated disorders, and limited data on long-term outcomes, it is not surprising that confusion and controversy have surfaced internationally regarding both diagnosis and clinical management. Decisions about follow-up frequency and therapy are especially difficult, along with explaining the condition to parents.[2] Although CF is a monogenic autosomal-recessive disorder caused by mutations in the gene encoding the CFTR protein, clinical heterogeneity causes diagnostic uncertainty in infants without symptoms and in older patients with milder phenotypes. Despite the advent of NBS for CF based initially on an elevated IRT, subsequent CF diagnoses can be challenging in many circumstances, such as when intermediate and inconclusive sweat chloride values occur,[7] when *CFTR* mutations of uncertain pathogenicity are detected,[5,8] and because of differential expression of *CFTR* or modifier effects.[9,10] Additionally, *CFTR* mutations that typically lead to classic cases of CF may simply not cause symptoms in infants and young children.[11]

In this era of NBS combined with enhanced genetic information,[5]it has become clear that the CFTR-associated phenotype ranges from the absence of disease symptoms to severe, life-shortening lung disease.[1,12] Perhaps even more perplexing is the fact that the number of CRMS cases identified in NBS programs varies depending on the screening protocol being used, the IRT method and cutoff values, and perhaps the region being screened (eg, in New York, the reported incidence of CRMS is approximately one-half the incidence of CF,[13] whereas in California, the reported incidence of CRMS is nearly 3 times the incidence of CF[14]). Nationally, according to CF Foundation Patient Registry (CFFPR) data from 2010 to 2012, it appears that there are 10 infants diagnosed with CF for each CRMS case registered.[13,15]

The biomarker IRT that made screening feasible is measured in dried blood spot specimens obtained during the first week of life and can be a sensitive screening test for CF, but a second tier test is needed to improve the sensitivity and specificity of the NBS protocol. Second-tier tests vary among programs and usually include DNA analysis.[16] When the screening is positive, the diagnosis of CF should be confirmed by measurement of chloride concentration in sweat, after clinical assessment, and may include expanded DNA analyses.[17] In some cases, the sweat chloride result may be intermediate or *CFTR* gene mutations may be identified with phenotypic consequences that are unclear.[5] However, in the US, nearly 20% of patients with CF are being enrolled in the CFFPR without sweat chloride test results.[13] This is disconcerting because as Amaral[18] recently stated "establishment of a definite CF diagnosis requires proof of CFTR dysfunction…." This requirement is no different than the laboratory criterion that has been used traditionally to confirm the diagnosis, but in the NBS era in which asymptomatic patients are evaluated routinely, less attention is being given in the US to the necessity of sweat testing. Perhaps this ironic phenomenon may be attributable to the greater difficulty of performing sweat tests in newborns.[19,20]

In addition, there may be some misinterpretation of the 2007-2008 consensus guidelines.[1] Although as part of the "Recommended CF Diagnostic Process for Screened Newborns" it states that "in the presence of 2 CF-causing mutations, a diagnosis of CF can be made," this statement is made for the category of "infants with a positive CF NBS result and sweat chloride values in the intermediate range (30 to 59 mmol/L)…" and elsewhere that "a positive screening test result… must be followed by referral for direct diagnostic testing (ie, sweat chloride test) to confirm a diagnosis of CF."[1] Also, it is emphasized that "CF cannot be diagnosed simply by the presence of 2 *CFTR* mutations; these 2 mutations must cause significant loss of function to result in a CF clinical phenotype."[1]

The report by Groves et al[6] in this issue of *The Journal* provides a framework for follow-up of infants with intermediate sweat chloride values. They found that 48% of those children screened who had an elevated IRT, one copy of p.508del *CFTR* mutation on NBS, and sweat chloride values of 30-59 mmol/L evolved to a formal CF diagnosis or delayed CF, which highlights the importance of continued follow-up of infants with intermediate sweat chloride levels. The authors are to be commended for generally maintaining follow-up, monitoring the condition of their patients, and repeating the sweat tests with excellent quantitative pilocarpine iontophoresis procedures. Interestingly, those patients found to have delayed CF had less pancreatic insufficiency, less colonization with non-mucoid *Pseudomonas aeruginosa*, milder obstructive lung dysfunction, and milder overall disease severity than the comparison CF group. Of concern were their nutritional outcome observations in which the body mass index and weight z scores initially were greater in the delayed CF cohort at 2 years of age but were not sustained, suggesting the onset of malnutrition.

Because of their design with a retrospective medical chart review, the authors acknowledge limitations in generalizability of their findings because of a possible bias by indication in their small sized cohort. However, the study most importantly addresses the potential likelihood (14/29 or 48%) of evolution to a formal CF diagnosis in those screened with intermediate/inconclusive sweat chloride values. Therefore, the authors conclude, and we agree, that close monitoring of these patients with intermediate sweat chloride values is warranted to determine whether these patients eventually develop further disease consistent with classical CF, a "phase shift," or maintain milder clinical phenotypes. The observations of Groves et al[6] in Australia differ quantitatively from those of Ren et al[13] in the US