Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive Diagnosis

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Objective An unintended consequence of cystic fibrosis (CF) newborn screening (NBS) is the identification of infants with a positive NBS test but inconclusive diagnostic testing. These infants are classified as CF transmembrane conductance regulator-related metabolic syndrome (CRMS) in the US and CF screen positive, inconclusive diagnosis (CFSPID) in other countries. Diagnostic and management decisions of these infants are challenges for CF healthcare professionals and stressful situations for families. As CF NBS has become more widespread across the world, increased information about the epidemiology and outcomes of these infants is becoming available. These data were reviewed at the 2015 CF Foundation Diagnosis Consensus Conference, and a harmonized definition of CRMS and CFSPID was developed.

Study design At the consensus conference, participants reviewed published and unpublished studies of CRMS/CFSPID and used a modified Delphi methodology to develop a harmonized approach to the definition of CRMS/CFSPID.

Results Several studies of CRMS/CFSPID from populations around the world have been published in the past year. Although the studies vary in the number of infants studied, study design, and outcome measures, there have been some consistent findings. CRMS/CFSPID occurs relatively frequently, with CF:CRMS that ranges from 3 to 5 cases of CF for every 1 case of CRMS/CFSPID in regions where gene sequencing is not used. The incidence varies by NBS protocol used, and in some regions more cases of CRMS/CFSPID are detected than cases of CF. The majority of individuals with CRMS/CFSPID do not develop CF disease or progress to a diagnosis of CF. However, between 10% and 20% of asymptomatic infants can develop clinical features concerning for CF, such as a respiratory culture positive for *Pseudomonas aeruginosa*. Most studies have only reported short-term outcomes in the first 1-3 years of life; the long-term outcomes of CRMS/CFSPID remain unknown. The European CF Society definition of CFSPID and the CF Foundation definition of CRMS differ only slightly, and the consensus conference was able to create a unified definition of CRMS/CFSPID.

Conclusions CRMS/CFSPID is a relatively common outcome of CF NBS, and clinicians need to be prepared to counsel families whose NBS test falls into this classification. The vast majority of infants with CRMS/CFSPID will remain free from disease manifestations early in life. However, a small proportion may develop clinical features concerning for CF or demonstrate progression to a clinical phenotype compatible with a CF diagnosis, and their long-term outcomes are not known. A consistent international definition of CRMS/CFSPID will allow for better data collection for study of outcomes and result in improved patient care. *(J Pediatr 2017;181S:S45-51).*

During the development of the 2008 cystic fibrosis (CF) diagnosis consensus guidelines, it was recognized that the increased implementation of newborn screening (NBS) had led to a new and complex diagnostic dilemma of infants with abnormal NBS tests but inconclusive sweat tests and/or DNA test results.[1] Rather than address this complex situation in the diagnostic guidelines, a separate CF Foundation consensus conference was convened to address

CF	Cystic fibrosis
CFFPR	CF Foundation Patient Registry
CFSPID	CF screen positive, inconclusive diagnosis
CFTR	CF transmembrane conductance regulator
CFTR-RD	CFTR-related disorder
CRMS	CFTR-related metabolic syndrome
ECFS	European CF Society
IRT	Immunoreactive trypsinogen
NBS	Newborn screening
PCP	Primary care provider

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Table I. Consensus recommendations related to CRMS/CFSPID

Statement numbers*	Consensus statements
16	The term CRMS is used in the US for healthcare delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS.
17	The term CRMS/CFSPID is reserved for individuals who screen positive without clinical features consistent with a diagnosis of CF.
18	The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either: • A sweat chloride <30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences *OR* • An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations
19	Children designated as CRMS/CFSPID should undergo at least one repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center.
20	Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms.
21	Children designated as CRMS/CFSPID can be considered for extended *CFTR* gene analysis (sequencing and/or deletion duplication testing), as well as CFTR functional analysis (NPD/ICM) testing to further define their likelihood of developing CF.
22	The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of CFTR (sweat chloride, and possibly NPD/ICM), *CFTR* genetic analysis, and clinical assessment by the CF clinicians caring for the patient.
23	Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies.
24	Research recommendation: Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow-up.

ICM, intestinal current measurement; *NPM*, nasal potential difference.
*Adapted from Farrell et al.[2]

this issue. An expert panel used the Delphi method and created a new diagnostic term, CF transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS) and recommendations for its management.[3] CRMS is the term used in the US to describe infants with elevated immunoreactive trypsinogen (IRT) levels, but with insufficient sweat chloride or genetic data to support a diagnosis of CF. Although this condition is not a metabolic disorder, the designation metabolic syndrome was established in part to have an *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* medical code (277.9) for US healthcare delivery system follow-up and billing purposes. However, CRMS has not been accepted in Europe and some other countries because of concern about the appropriateness of the term and a feeling that it was difficult for families to understand. Thus, a similar term, CF screen positive, inconclusive diagnosis (CFSPID), was developed in a Delphi process[4] by the European CF Society (ECFS) Neonatal Screening Working Group and introduced recently in Europe as an alternative to CRMS.[5]

The planning committee for the 2015 Diagnosis Consensus Conference recognized that with the increasing use of CF NBS worldwide, CRMS and CFSPID have become important aspects of the CF diagnostic process. Therefore, the conference included a session to review recently published and unpublished data on populations with CRMS and CFSPID. An important goal of the conference was to develop a consensus to unify the definition of CRMS and CFSPID that could allow for collection of data from populations around the world and increase our understanding of the epidemiology and outcomes of CRMS/CFSPID. At the conclusion of the conference, consensus recommendations were crafted and agreed upon by electronic survey (**Table I**).

Harmonization of US and ECFS Terminology

In the US, the expert consensus panel specifically created a term that did not imply the infant has CF, whereas still acknowledging that these infants required follow-up by CF specialists.[3] CRMS (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision* code E88.89) was defined as an infant with hypertrypsinogenemia at birth who is asymptomatic, and who has either: (1) persistently intermediate sweat chloride levels (30-59 mmol/L if age <6 months or 40-59 mmol/L if age ≥6 months) and fewer than 2 CF-causing *CFTR* mutations; or (2) sweat chloride concentration <30 mmol/L and 2 *CFTR* mutations with 0 to 1 known to be CF-causing.

In Europe and some other countries, especially when international coding is not required for healthcare delivery, expert consensus differed slightly on how to define this group. In the initial ECFS consensus process,[4] it was recommended that these infants should not have a designation, but in the second exercise 5 years later,[5] it was clear that the majority of respondents believed a designation was needed. In the subsequent voting exercise (including CRMS as an option), there were 2 clear favorites: CF inconclusive diagnosis and CFSPID. An expert panel decided to amalgamate the 2 terms, and CF screen positive, inconclusive diagnosis (CFSPID) reached high levels of agreement in the subsequent round of the Delphi exercise, creating a category for infants who are asymptomatic, with hypertrypsinogenemia at birth,[5] and have either: (1) 0 or 1 *CFTR* mutations, plus intermediate sweat chloride (30-59 mmol/L); or (2) 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences, plus a normal sweat chloride (<30 mmol/L).

The differences between the definitions of CRMS and CFSPID are minor and resolved by the improved characterization of *CFTR* mutations as disease-causing by the CFTR2 project. The CF Foundation recognizes that CFSPID is a term that may be helpful in describing this complex situation to parents and families. However, the term CRMS will continue to be required for entry of this group of individuals into the US healthcare system. Recognizing the 2 groups as 1 will