



Original Article

Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID)

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ABSTRACT

Over the past two decades there has been considerable progress with the evaluation and management of infants with an inconclusive diagnosis following Newborn Screening (NBS) for cystic Fibrosis (CF). In addition, we have an increasing amount of evidence on which to base guidance on the management of these infants and, importantly, we have a consistent designation being used across the globe of CRMS/CFSPID. There is still work to be undertaken and research questions to answer, but these infants now receive more consistent and appropriate care pathways than previously.

It is clear that the majority of these infants remain healthy, do not convert to a diagnosis of CF in childhood, and advice on management should reflect this. However, it is also clear that some will convert to

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a CF diagnosis and monitoring of these infants should facilitate their early recognition. Those infants that do not convert to a CF diagnosis have some potential of developing a CFTR-RD later in life. At present, it is not possible to quantify this risk, but families need to be provided with clear information of what to look out for. This paper contains a number of changes from previous guidance in light of developing evidence, but the major change is the recommendation of a detailed assessment of the child with CRMS/CFSPID in the sixth year of age, including respiratory function assessment and imaging. With these data, the CF team can discuss future care arrangements with the family and come to a shared decision on the best way forward, which may include discharge to primary care with appropriate information. Information is key for these families, and we recommend consideration of a further appointment when the individual is a young adult to directly communicate the implications of the CRMS/CFSPID designation.

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1. Introduction

The introduction of newborn bloodspot screening (NBS) for cystic fibrosis (CF) has resulted in earlier diagnosis and better outcomes for children with CF [1]. In most cases the diagnosis of CF after a positive NBS result is straightforward. Identification of infants with an inconclusive diagnosis after a positive NBS result is an increasingly recognised outcome, which leads to uncertainty for both families and healthcare professionals [2]. The approach to the management of these infants is evolving with increased experience and reporting of outcomes. It is important that strategies are based, whenever possible, on evidence of benefit for the child and family. To default these children to a full CF care pathway is not appropriate, but it is equally important that the potential risks that these infants face are recognised and addressed.

2. Aims and objectives

The guidance presented represents the views of the European CF Society (ECFS) Neonatal Screening Working Group (NSWG) and other experts from across the globe. The preliminary recommendations were drafted by a core group (JB, CC, AM, KWS) and then adapted following the comments of all other authors (core committee members and experts in the field). We aimed to present an update on the considerable developments in the field since the designation, CF Screen Positive, Inconclusive Diagnosis (CFSPID), was proposed by the group in 2014 [3]. There is now a global harmonised definition, described below, and emerging evidence on which to base these recommendations. It is clear that there is still much work to do in this field and evidence needs to be consolidated on the outcome of infants in this situation. The proposals in this paper are an evolution of earlier recommendations and hopefully represent a balanced approach to these infants and their families.

3. Global harmonisation of designation

There has been some international variance over the designation for infants with an inconclusive diagnosis after NBS for CF, and some debate as to whether a designation is even necessary for these infants, or whether by applying a label, the infant will be exposed to an increased risk of inappropriate medicalisation. In the US, a consensus group proposed the designation, 'cystic fibrosis transmembrane conductance regulator (CFTR)-related metabolic syndrome' (CRMS) [4]. This term was established to be consistent with the existing categorization of CF within the International Classification of Diseases (ICD). The ICD is important for ensuring consistent coding of conditions across the globe and also underpins the medical code system in the US, which is used for insurance and billing purposes [5]. This designation has not been widely embraced outside of the US, for a number of reasons; 1) there is concern over the use of the term syndrome, as these infants are by

definition healthy, 2) the use of "metabolic", which reflects the elevated immunoreactive trypsinogen, is not appropriate in this situation and 3) concern that the term may lead to over-medicalization of these children. In Europe, a consensus exercise undertaken by the ECFS NSWG resulted in the term 'CF Screen Positive, Inconclusive Diagnosis' (CFSPID) [3]. In addition, the European exercise divided CFSPID infants into two groups; (A) a normal sweat chloride (<30 mmol/L) and 2 CFTR mutations, at least one of which has unclear phenotypic consequences and (B) an intermediate sweat chloride (30–59 mmol/L) and one or no CFTR mutation. Guidelines for early management were slightly different for each group, reflecting increased concern of the consensus group for infants with an intermediate sweat chloride. Although the abbreviation CFSPID provides a clear description of the situation, it does include the letters "CF" and has generally been shortened to CF-SPID, which is not ideal and may imply a closer link to a CF diagnosis than intended.

A global harmonisation process was undertaken in 2016 to provide a consistent international approach and definition [6–8]. It was decided that these infants should be classified as CRMS/CFSPID and this term now supersedes both CRMS and CFSPID [6,7]. There is recognition that this is an unwieldy designation and some expectation that CFSPID may be used when discussing this situation with families, especially in Europe [7].

The harmonised definition:

An asymptomatic infant with a positive NBS result for CF and either a sweat chloride value <30 mmol/L and two CFTR variants at least one of which has unclear phenotypic consequences OR an intermediate sweat chloride value (30–59 mmol/L) and one or zero CF causing variants [8].

The term DNA "variant" is now preferred to "mutation", which was used in the original publication [9]. The accurate definition and designation of infants with CRMS/CFSPID is vital and facilitates the establishment of worldwide databases to monitor long-term outcomes, as well as the implementation of consistent appropriate care pathways.

For the harmonised definition, an infant with the designation of CRMS/CFSPID may have two CFTR variants and an intermediate sweat chloride concentration, if one of the variants has unclear or varying phenotypic expression. This is a change from the previous European definition [3].

4. The characterisation of CFTR variants

Information about variant classification and characterisation can be obtained from a number of sources most notably the CFTR-2 website (cftr2.org). The CFTR-2 project has collected information from over 89,000 CF patients, and uses clinical, functional, and penetrance analysis to evaluate the disease liability of more than 400 CFTR variants. At present, approximately 1600 variants, mostly rare, could not be assessed because of lack of data. Another resource is CFTR-France, which has adopted a different methodology

to assess variant behaviour from a database including not only CF but other clinical phenotypes (<https://cftr.iurc.montp.inserm.fr/cftr>) [10]. Occasionally the conclusions of these two resources may differ [11]. On the whole these exercises have represented a major step forward in the ability to characterise *CFTR* variants and communicate outlook with families, which has had a direct and considerable impact on the evaluation of infants with CRMS/CFSPID.

The following classification has been proposed by CFTR-2 for variant types and these are now widely accepted in the field:

- CF causing: two of these variants *in trans* cause CF.
- Variants of Varying Clinical Consequence (VVCC): some individuals with this variant and a CF causing variant on the other allele will have CF and others will not have a diagnosis of CF (some may develop a CFTR related disorder (CFTR-RD); described in later section).
- Non-CF causing: when there is a CF-causing variant on the other allele these variants do not cause CF, but may rarely be associated with a CFTR-RD. They are more likely to have no clinical consequences.
- Variants of Unknown Significance (VUS): insufficient data are available to determine the phenotypic pattern associated with this variant.

The detailed characterisation of *CFTR* variants over the past ten years has been a major advance with direct impact on the evaluation and management of CRMS/CFSPID infants [12,13]. The determination of a variant as “CF causing” provides clarity, particularly for those variants that are associated with a less severe phenotype. However, for some variants there is an acknowledgement that diagnostic outcome is variable and that for some individuals there is no clinical consequence. A good example of a VVCC is c.3454G>C (legacy name, D1152H). There are reports linking this variant with significant clinical features associated with CF later in life (most notably pancreatitis and isolated bronchiectasis), but a recognition that for some individuals this variant had no clinical consequence [14]. Girodon and her French colleagues have recently provided useful clarity on the penetrance of VVCC and this work will provide further evidence to inform the counselling of families [11]. Despite the advances in CFTR variant characterisation, there remains an absolute requirement for physiological assessment of these infants and sweat testing remains the gold standard undertaken in a laboratory with good experience and capability to measure sweat chloride concentration. The additional diagnostic role of other electrophysiological tests in young children, such as a nasal potential difference (NPD) or intestinal current measurements (ICM), is less clear now with the advances in CFTR characterisation. French guidelines advocate electrophysiological measurements if available, either directly by NPD measurement or *ex vivo*, by ICM [15]. NPD is extremely challenging in pre-school children but ICM is possible if laboratory resources are available. Preliminary evidence suggests that intestinal organoids may have a role as a CFTR bio-marker in the characterisation of infants with CRMS/CFSPID, but neither ICM or organoids are sufficiently validated, at present, to recommend routinely in the evaluation of these infants [16].

Although CFTR-2 and CFTR-France have characterised several hundred *CFTR* variants, many of the 2000+ variants that are reported on CFTR-1 (an inclusive database of *CFTR* variants) have not been characterised and likely never will, because they occur at a low frequency. Programmes that employ extended *CFTR* gene sequencing often identify VUS, as these occur regularly in the human genome.

A prevalent *CFTR* variant, c.350G>A (legacy name, R117H), is associated with two common haplotypes, reflecting different lengths of the poly T tract before exon 9. When this missense variant is associated with the 5T variant, the impact on production of mRNA

results in a “CF causing variant”, but when associated with the 7T variant, the combination is a VVCC. Population studies in France confirmed that a significant number of individuals with R117H/7T and a CF causing variant on the other allele will not demonstrate a clinical phenotype [17]. Infants with a positive NBS result and this genotype (R117H/7T and a CF causing variant *in trans*) have a CRMS/CFSPID designation, unless they have a sweat chloride concentration greater than 59 mmol/L.

Some residual function variants, including R117H, have now been approved for modulator therapy with ivacaftor (<https://www.ema.europa.eu/en/medicines/human/EPAR/kalydeco>). To be eligible for this therapy, an infant with R117H/7T identified after a positive NBS result must have a raised sweat chloride concentration to have a diagnosis of CF. Infants with CRMS/CFSPID should not be prescribed this therapy, as they do not have a diagnosis of CF.

In addition to the R117H/5T haplotype, the 5T variant can occur in isolation and is recognised in some infants with CRMS/CFSPID. Retrospective data from a large Californian cohort suggest that the penetrance of this variant depends on the presence of an increased number of TG repeats in a separate part of the gene (with 13TG repeats having much higher penetrance to a CF phenotype than 12 or 11) [18].

5. CFTR-related disorder (CFTR-RD)

There are some clinical conditions that are recognised to be associated with abnormality of the *CFTR* gene, but are not CF. The best characterised of these is congenital bilateral absence of the vas deferens (CBAVD), a well-recognised cause of infertility [19]. Men with this condition are identified to have a high frequency of *CFTR* variants, often VVCCs [19]. Other conditions linked to CFTR dysfunction include pancreatitis (chronic and acute recurrent), isolated bronchiectasis and rhino-sinusitis [20]. In 2011, Bombieri and colleagues published an international consensus on the classification of CFTR-related disorders; conditions that present clinically, mainly in adult life, but do not fulfil the criteria for a diagnosis of CF [21]. Infants with a CRMS/CFSPID designation may have an increased risk of developing a CFTR-RD, even if they remain healthy during their childhood, as the variants reported with CFTR-RD are regularly seen in infants with CRMS/CFSPID [11,22].

CRMS/CFSPID and CFTR-RD are quite distinct designations, one a consequence of a positive NBS test and the other arising from clinical features. For children with CRMS/CFSPID who develop clinical features consistent with CF, it is debated as to whether they are re-classified as CFTR-RD or CF. Most importantly, these children should receive appropriate care regardless of designation. Although these children may not have the typical features and severity of CF, they have revealed themselves as being at risk through their progression.

The CFTR-RD designation, determined in 2011, is currently being re-evaluated in light of developments in variant characterisation and increased information on clinical progression. This may have an impact on the designation of infants with CRMS/CFSPID, who develop clinical features consistent with CF, but at present, it is important that families (and individuals) are aware of the risks of developing the well characterised CFTR-RDs, CBAVD and pancreatitis. The suggested communication with the family is described later (Fig. 1).

6. Frequency of CRMS/CFSPID

All CF NBS programmes, regardless of the protocol used, can result in the identification of infants with inconclusive diagnosis, including programmes that are limited to biochemical tests. However, the frequency of CRMS/CFSPID recognition increases for protocols that use DNA analysis and there is good evidence that the

Advice to young people with a CRMS/CFSPID designation regarding CFTR-RD

An information sheet should include the following:

- *Shortly after birth, you had a screening test for a condition called cystic fibrosis (CF).*
- *Your screening test was positive, but then subsequent tests showed that you did not have CF.*
- *This situation is described as CF Screen Positive, Inconclusive Diagnosis (CFSPID).*
- *This information outlines what this means for you now that you are a healthy young adult.*
- *The proper name for the gene affected in people with CF is the CFTR gene*
- *CFTR stands for “Cystic Fibrosis Transmembrane Conductance Regulator”*
- *There are some conditions that have been recognised that are associated with mild abnormality of the CFTR gene, but are not cystic fibrosis*
- *These conditions have been called CFTR-related disorders*
- *The two most clearly characterised CFTR-related disorders are congenital bilateral absence of vas deferens (CBAVD) and pancreatitis.*
- *The risk of having these conditions in the general population is very low*
- *The risk is increased for young people who had a designation of CRMS/CFSPID, but the extent of the increase is not yet known.*

What does this mean for you?

- *CBAVD is a cause of infertility for men, which is easy to diagnose if considered.*
- *Men with CBAVD produce normal sperm and are able to have children through assisted fertilisation.*
- *Pancreatitis is associated with episodes of severe abdominal pain.*
- *There is a straight forward test for pancreatitis and it is important to describe your previous CFSPID designation with a doctor if you have severe abdominal pain you could show them this information sheet.*

If you are concerned about these conditions or would like further information, don’t hesitate to discuss with your CF specialist team or primary care physician (Primary Care Physician or General Practitioner)

Fig. 1. Advice to young people with a CRMS/CFSPID designation regarding CFTR-RD.

proportion of CRMS/CFSPID infants recognised compared to those with a CF diagnosis increases for protocols that use more extensive DNA analysis, for example gene sequencing [23]. A European survey of the performance of nine national programmes in 2014 reported, in total, 535 children with CF and 99 children with a CRMS/CFSPID designation (ratio of CF:CFSPID, 5.4:1) [24]. Most reported limited CRMS/CFSPID numbers, but one country using extended gene sequencing reported 55 CRMS/CFSPID cases in the year of the survey. The ratio of CF:CFSPID ranged widely from 32:1 (Ireland) to 1.2:1 (Poland) [24]. This variation is also explained to a lesser extent by the different population (local variant heterogeneity) and by the different algorithms used (especially use of pancreatitis associated protein (PAP) as an additional biochemical marker to immune-reactive trypsinogen (IRT) to reduce CRMS/CFSPID recognition) [24]. The use of larger DNA variant panels may improve the sensitivity of a NBS programme, but the larger the panel the greater the probability of obtaining inconclusive diagnoses, unless the panel is restricted to CF causing variants [24].

NBS protocols that do not employ DNA analysis will recognise significantly fewer infants with CRMS/CFSPID, but often at the

expense of performance with respect to positive predictive value (PPV) and sensitivity. A potential strategy to improve the performance of an IRT protocol is the addition of a second biochemical test, pancreatitis associated protein (PAP). Measuring these two biochemical markers in parallel can improve PPV, but at the expense of sensitivity. Hybrid protocols that incorporate IRT, PAP and DNA analysis can be designed that improve performance but still minimise CRMS/CFSPID recognition [25].

For NBS protocols that incorporate extensive DNA analysis, a strategy to reduce CRMS/CFSPID recognition is to only report variants that are recognised as CF causing (although most programmes would continue to include VVCCs) [26,27].

There are other strategies to minimise CRMS/CFSPID recognition. These include incorporating faecal pancreatic-elastase-1 (FE-1) measurement for infants with one CF causing variant when a sweat test is not successful, rather than reflexing to more extended DNA analysis at that point, before the repeat sweat test. Infants with a reduced FE-1 would be considered presumptive CF and treatment established. For infants with a normal FE-1, a further sweat test is organised, but no extended DNA analysis [28].

Table 1
Summary of recent studies of CRMS/CFSPID [from reference 2].

	Prospective studies		Retrospective studies				Registry study
	Ooi et al. [29]	Munck et al. [30]	Kharrazi et al. [31]	Groves et al. [32]	Levy et al. [33]	Terlizzi et al. [34]	Ren et al. [35]
Study design	Prospective case control	Prospective case control	Retrospective	Retrospective case control	Retrospective cross sectional	Retrospective	CFF registry
Country	Canada, Italy	France	USA California	Australia	US Wisconsin	Italy Tuscany	US
Birth period	2007–2013	2002–2009	2007–2012	1996–2010	1994–2012	2011–2016	2010–2012
Follow up duration (y)	Median 2.2	Mean 7.4	Mean 4.5	10	8	Median 0.6	1
Number CF	80	63	325	225	300	32	1540
Number CRMS/CFSPID	82	63	553	29 ^a	57	50	309
CF:CRMS/CFSPID	1.8:1	6.3:1	0.67:1	7.8:1	5.2:1	0.64:1	5:1
Conversion to CF, N (%)	9 (11)	28 (44)	20 (5.8)	14 (48) matched to CF	NA ^c	5 (10)	NA ^c
Increased SCC ≥ 60 mmol/L	2	8	17	2 ^b		5	
2 CF causing mutations	4	12	0	0		0	
Both criteria	3	8	0	0		0	
Other criteria	0	0	3	12		0	
Age at conversion (y)	Mean 1.8 $\pm$ 1.2	Unknown	Mean 2.5 $\pm$ 1.4	Median 0.19 (0.1–4.76)		Median 2 (0.2–4)	
<i>Pseudomonas aeruginosa</i> (%)	12	24	Unknown	78.6	39	25 ^d	10.7
Pancreatic insufficiency (%)	0	0	15	14	0	0	4.5
F508del/R117H (%)	19.5	43	Unknown	29	63	0	26

CF: Cystic fibrosis, CFTR: CF transmembrane conductance regulator (gene), CFMS: CFTR-related metabolic syndrome, CFSPID: CF screen positive, inconclusive diagnosis,

SCC: Sweat Chloride Concentration.

^a Definition slightly different from CRMS/CFSPID

^b Only 8/14 had a repeated sweat test.

^c NA: non applicable.

^d Only 8/50 had swab culture.

7. Studies reporting the clinical outcome of infants with CRMS/CFSPID

The reported rate of conversion or reclassification from a CRMS/CFSPID designation to a CF diagnosis varies from 6% to 48% in published studies (Table 1). The use of a wide variety of protocols is the key factor to explain these different conversion rates. Programmes with limited DNA analysis (for example, France and Australia) recognised fewer infants with CRMS/CFSPID but proportionally these infants were more likely to convert or be reclassified to a CF diagnosis [2]. Other reasons for the discrepancy in CF conversion rates among studies are 1) the different definitions of an inconclusive diagnosis and the final CF diagnosis, 2) different interpretation of individual *CFTR* variants (previously VUS and later classified as CF causing) and 3) differing durations of follow-up [2].

Data on the outcomes of infants with CRMS/CFSPID have been derived from prospective studies [29,30], retrospective studies [31–34] and registry data [35].

7.1. Prospective studies

- A Canadian/Italian collaboration prospectively evaluated and monitored 82 infants with CFSPID and 80 with CF after a positive NBS result from seven CF clinics in three provinces in Canada (Ontario, British Columbia and Alberta) and one in Italy (North East) for a total of 3 years [29]. All children with CFSPID were pancreatic sufficient and had significantly less frequent clinical symptoms (wheeze, cough, constipation and abdominal pain). Eleven percent (9/82) of children with CFSPID fulfilled the diagnostic criteria for CF during the follow-up period: in two children this was only based on their sweat chloride concentration increasing into the diagnostic range; in seven the reclassification was a result of the variant becoming recognised as CF causing. In total, five children developed an abnormal sweat chloride concentration at a mean age of 21.3 (SD, 13.8) months.
- A multicentre study performed in France over ten years evaluated 63 infants with an inconclusive diagnosis after NBS un-

til they were in school (mean age of 7.4 (SD, 1.4) years) and compared them with a 1:1 matched cohort of infants with CF diagnosed by NBS [30]. The term CFSPID was only developed halfway through the study, so not applied to all infants, although retrospectively we can assume they fulfilled this definition. All children with CRMS/CFSPID were pancreatic sufficient, and 44% (28/63) of them converted to a delayed CF diagnosis: 8 based on a positive sweat chloride concentration, 12 reclassified due to the identification of two CF-causing variants, and 8 for both reasons. The children had thorough clinical evaluation and investigation through the study and despite the significant conversion/re-classification rate to a CF diagnosis, the results suggest they had little clinical evidence of CF disease.

In both prospective studies, children with CRMS/CFSPID had significantly lower median IRT values compared to children with CF (77 μ g/L versus 144 μ g/L and 97 μ g/L versus 166 μ g/L, respectively). [29,30] There was no difference in initial IRT between those who converted to a CF diagnosis and those who remained CRMS/CFSPID [29,30] although a later update from the Canadian/Italian group suggested some predictive value of initial IRT value to conversion/reclassification of CRMS/CFSPID to CF [36]. The authors of both studies emphasise that the majority of these children were well, and clinical symptoms did not appear to be a significant discriminator for the subsequent diagnosis of CF during the first 3 years of life. In both studies, children with CRMS/CFSPID (compared to CF) showed significantly lower positive oropharyngeal culture rates for *Pseudomonas aeruginosa* (12% vs. 31% and 24% vs. 82%) and *Staphylococcus aureus* (40% vs. 70% and 68% vs. 90%). During the multi-year observation phase of the French study, 70% (44/63) of the children with CRMS/CFSPID developed transient respiratory symptoms which were not specific for CF. Those who later received a CF diagnosis had similar initial sweat chloride concentration and no clinical differences at final assessment compared to those who did not convert to CF.

The mean age of conversion in the Canadian/Italian study [29] was 1.8 (SD, 1.2) years and the authors recommend monitor-

ing of these children with CRMS/CFSPID with serial sweat testing at least annually until the 3rd year of life, with two years being the most discriminatory age for making a diagnosis of CF. In the French study there was no precise information on the age of conversion, but based on their data the authors suggest a less intensive approach for the management of these infants compared to those with a CF diagnosis, and consideration of a discharge from the CF Centre after 6 years if the child has not converted to CF [30]. However, they emphasize that the primary care physician should remain vigilant especially for unexplained recurring respiratory symptoms.

7.2. Retrospective studies

- The first 5 years (2007–12) of the Californian CF NBS programme were evaluated retrospectively [31]. Of the 345 infants designated with CRMS, 5.8% (20) had their diagnosis changed to CF after the age of 6 months, mainly due to a positive sweat test result (≥ 60 mmol/L). The mean follow-up was 4.5 years and mean age of diagnosis 2.5 years (SD, 1.4). All but one of these children were classified as pancreatic sufficient; one infant had a borderline faecal elastase but was not prescribed pancreatic enzyme replacement therapy.
- A retrospective review of children with a positive NBS result (elevated IRT and one copy of c.1521_1523delCTT (legacy name, F508del)) and intermediate sweat chloride values over 15 years (1996–2010) in an Australian centre demonstrated a conversion rate to a CF diagnosis of 48% (14/29) [32]. The diagnosis was based on a subsequent abnormal sweat chloride level (2), pancreatic insufficiency (4) recurring respiratory symptoms (8). The CF diagnosis was made at a median age of 69 days (0.19 years, range 0.1–4.76) compared to 44 days of matched children with a CF diagnosis (0.12 years, range 0.07–0.31), which suggests this re-classification to CF is more a delayed CF diagnosis following assessment as a result of the protocol employed. The authors highlight that the CRMS/CFSPID classification was difficult to apply in their retrospective study and most of these children had repeated sweat test only when clinically indicated. Another drawback of this study was the high rate of lost to follow-up by age 10 (28%). The implication is that this represents a selection bias towards sicker children with the total non-CF group possibly being healthier than described. The DNA was initially F508del alone and then from 1999, a limited 14 variant panel. These data do not reflect the characteristics of CRMS/CFSPID infants recognised following more extensive DNA testing.
- A retrospective cross-sectional evaluation in the US state of Wisconsin investigated clinical and laboratory descriptors in a physician defined cohort of children (most with a positive NBS result) to determine the robustness of classification in a “real world situation” [33]. Of the 376 infants with a positive NBS result, 300 (80%) were diagnosed with CF, 57 (15%) with CRMS, and 19 (5%) with a “CFTR-RD”, which was defined as a symptomatic child with CRMS, but symptoms were not specified. The term “CFTR-related disorder” (CFTR-RD) used by the authors is quite confusing as it has been earlier used to describe older patients with a clinical phenotype that likely results from CFTR dysfunction but does not fulfil the diagnostic criteria for CF [37]. All the reported infants with CRMS and “CFTR-RD” were pancreatic sufficient, and the authors do not give a number of how many infants with CRMS/CFSPID converted to CF. Children with CRMS/CFSPID had significantly lower sweat chloride values at diagnosis compared with the CFTR-RD infants (35 vs. 43 mmol/L), and both differed significantly from CF diagnosis (105 mmol/L). Twenty two percent of children with the label “CFTR-RD” and 27% with CRMS/CFSPID had a normal first sweat test; 16/18 (89%) of them had at least one R117H/7T variant.

- A retrospective study from a region of Italy (Tuscany) evaluated 50 infants with an early CRMS/CFSPID designation from 2011 to 2016 [34]. All these infants were pancreatic sufficient, all had an intermediate initial sweat chloride concentration and many did not have two CFTR variants recognised (44%). After a median follow-up of 6 months, and after full CFTR sequencing if < 2 variants originally detected, 37/50 (74%) had a conclusive outcome; 5 (10%) had CF with a final sweat chloride of > 60 mmol/L, 17 (34%) were classified as healthy and 15 (30%) were designated as healthy carriers. Thirteen (28%) still had an inconclusive diagnosis with a CRMS/CFSPID designation.

7.3. Registry studies

Data from the CFF Patient Registry demonstrated a rate of re-classification of children with CRMS/CFSPID to CF of 11% [35]. This was mainly due to the expansion of the number of variants classified as CF causing by the CFTR-2 project (www.cftr2.org) and/or subsequent elevation of sweat chloride concentration. In contrast, at their local centre, 41% of infants with CRMS/CFSPID were incorrectly entered in the registry as CF, despite not fulfilling the diagnostic criteria, again highlighting the need for clear designation of these infants [8].

8. What do these studies tell us about the outlook for infants with CRMS/CFSPID

- 1) The evolution of these infants can follow a number of pathways. We have used the term conversion when a diagnosis of CF is established for clinical reasons (i.e., an evolving sweat test result or clinical features). We use the term re-classification if the diagnosis relates to new information from CFTR-2 about a specific variant.
- 2) The main reasons for an infant with a CRMS/CFSPID designation to be subsequently diagnosed with CF are conversion with a positive sweat test (> 59 mmol/L) and/or re-classification because of reassignment of CFTR variants as CF causing [30,38]. In the case of re-classification, this reflects an increase in information available, rather than a change in the clinical picture. In reality, these children always had CF [38].
- 3) The development of clinical features leading to a CF diagnosis is reported but is not a common cause of conversion.
- 4) The use of extended gene sequencing as part of the NBS protocol results in an increased proportion of CRMS/CFSPID designations compared to CF diagnoses, if all CFTR variants are reported.
- 5) Children with CRMS/CFSPID designation who convert to a CF diagnosis are not clearly distinguishable from those who do not on the basis of clinical symptoms; all these children are pancreatic sufficient. Studies of longer term outcomes are needed (beyond ten years of age).
- 6) Infants with a CRMS/CFSPID designation have lower initial IRT values than infants with a CF diagnosis. It remains unclear whether, at the individual level, the IRT level can predict which infants with CRMS/CFSPID will convert to a CF diagnosis [29,36].
- 7) Comparing different cohort studies, the evidence suggests that infants with an initial intermediate sweat chloride concentration are more likely to convert to a CF diagnosis than those in whom the initial value was normal [30–32].
- 8) Although included in the initial European guideline on evaluation of infants with CRMS/CFSPID, the role of electrophysiological measurements in determining the outcome for these infants remains unclear [39].
- 9) The risk for infants with CRMS/CFSPID of developing a CFTR-RD cannot be determined with the data available. There is a

theoretical risk, as the genetic information from adults with CFTR-RD demonstrates high frequency of variants that occur commonly in infants with CRMS/CFSPID. At present, we cannot quantify these risks for infants with CRMS/CFSPID and long-term collection of data is imperative to answer this question.

9. How should we communicate a CRMS/CFSPID designation to parents?

Providing clear information to families is an important part of the NBS process to minimise unnecessary stress and anxiety [40]. To date, there is no internationally accepted consensus on the optimal approach to this [41]. Communicating positive NBS results for any condition is not an event but a process that starts from the moment the result is identified as being above the agreed 'cut off' and ends when the parents are given a definitive diagnosis for their child [42]. As a positive NBS result in itself is not diagnostic, and further tests are required to confirm or refute a definitive diagnosis, this represents a period of huge uncertainty for families.

In the process of communicating to the parents/carers of an infant with CRMS/CFSPID, it is important,

- To communicate clearly and consistently with parents in order to maintain confidence in health care professionals and systems.
- To acknowledge that this is a challenging situation.
- To acknowledge that we do not know for sure about the long term outcomes, and only ongoing studies and registry data will bring a clearer answer.
- To bear in mind, that when a healthcare professional is discussing the CRMS/CFSPID designation with the family, they should not present this as a good result compared to a diagnosis of CF. Be aware that the family do not consider this a good outcome.
- To be clear that the positive NBS result is the start of a journey that needs diagnostic clarification (to avoid highs and lows during this journey for the family).
- To provide information, if local data are available, on the proportion of children that may convert to a CF diagnosis.
- To explain the purpose of regular clinic visits in the pre-school years to monitor progress and recognise clinical features associated with CF, and that these may evolve over a long timeframe.
- To educate the parent/carers and primary care physician as to what symptoms to be alert to and when to seek an opinion from the CF team.
- To maintain a healthy lifestyle for this infant in the context of a healthy family
- To emphasize that CRMS/CFSPID infants are well, and most will remain well.
- To outline the risk for a CRMS/CFSPID child of developing or manifesting a CFTR-RD in later life (Fig. 1).

Communication with the family needs to be consistent, ideally by the same team over the years and avoid mixed messages. The support of a Clinical Psychologist embedded within the CF team, is a key component of the communication strategy. In addition, the parent/carers should have access to genetic counsellors for further support and to outline options for reproductive decision making.

10. Short and long-term management

10.1. The rationale for monitoring these infants

Variants tend to show a CFTR function gradient, with those CF causing variants having the larger functional impairment, VVCC milder degrees of dysfunction, and non-CF causing variants partially or even completely preserved function. This implies that the

CFTR genotype could have prognostic implications: for example, an infant with a CF causing variant and a VVCC might have a greater risk of developing significant clinical manifestations than a baby carrying a VVCC and a non-CF causing one. This should be taken into account when a new CRMS/CFSPID infant is identified but also when the possible discharge of a six-year-old well child with sweat chloride concentration below 60 mmol/L is discussed.

10.2. Management guidance

There has been progress over the past ten years with respect to the evaluation, designation and early management of infants with CRMS/CFSPID [3,4,6–8,15,43]. There is less clear evidence on longer term management [44]. There are no studies supporting the routine use of CF therapies for the treatment of CRMS/CFSPID infants and there is potential for iatrogenic harm. There is debate on the length of follow-up of CRMS/CFSPID infants. Below we outline new guidance on the management of CRMS/CFSPID infants based on emerging evidence and consensus of the NSWG core committee (Table 2). This advice reflects a balanced approach derived from the views of experts that sit on both ends of the spectrum with respect to the management of these children.

10.2.1. Initial assessment

The assessment should include clinical evaluation, sweat testing, extended CFTR analysis if the genotype is incomplete (with a check-up for updates in clinical relevance at www.cftr2.org) and collection of stool sample for measurement of faecal elastase-1 (FE-1) [3,4,28]. Clinical assessment includes respiratory, abdominal and nutritional assessment (Table 2). The sweat test should be undertaken in a centre with considerable experience and the ability to perform sweat chloride measurement. Parents should be fully informed about the possible outcomes of CRMS/CFSPID and the plans for future monitoring, where and how often, including the more detailed assessment that will be undertaken at six years of age (see later section). The parents should be offered genetic counselling to support future reproductive decision making. The primary care physician should receive a detailed report, including reasons they should consider for prompt referral, notably a persistent cough or, less likely, problems with weight gain. A sweat test and evaluation of older siblings should be discussed with the family and undertaken if felt appropriate. DNA analysis of the siblings may be considered, taking into account the variant attitudes towards genetic testing of healthy children in different countries. The importance of a healthy lifestyle for the whole family should be reiterated, especially avoidance of cigarette smoke. The assessment and management of these infants should be undertaken by a physician with specialist CF knowledge. There is varied practice with respect to the location of these consultations; in a CF centre, a CF clinic environment or non-CF clinic. Prevention of potential cross-infection must be a priority during all hospital appointments, and this should inform the best local practice [3,4].

10.2.2. Monitoring and further evaluation in the first two years

The frequency of clinical review in the first two years will be dependant on the well-being of the infant and the anxieties and perceptions of the parent/carers [3,4]. Initial clinic visits may be decreased to an annual visit if the family feel confident and the infant is well, gaining weight appropriately. Data from the French prospective study do not support routine respiratory culture or imaging for infants with CRMS/CFSPID who are well in the first year of life. A sweat test should be repeated in a centre with considerable experience at six months and two years of age. A sweat test at 12 months may be considered appropriate, and can be reassuring for parents, but data from prospective studies suggest that

Table 2
Follow-up of children with CRMS/CFSPID.

	Initial assessment	6 months of age	12 months of age	2 years of age	3 years of age	4 years of age	5 years of age	6 years of age **
Diagnostic testing *								
Sweat chloride concentration	X	X	c	X	c	c	c	X
Extended <i>CFTR</i> analysis	X							c
Check for updates in clinical relevance of <i>cftr</i> variants at www.cftr2.org	X	X	X	X	X	X	X	X
Fecal elastase-1 measurement (stool assessment)	X	c	X	c	c	c	c	c
Care Management								
Inform GP/Paediatrician about CRMS/CFSPID (or change of diagnosis)	X	X	X	c	c	c	c	X
Provide explanations to parents on the follow-up (discuss the potential outcomes)	X	X	X	X	X	X	X	X
Genetic counselling	X							c
Respiratory assessment: history (cough, infections), including auscultation, RR	X	X	X	X	X	X	X	X
Abdominal assessment: history and examination	X	X	X	X	X	X	X	X
Nutritional assessment: weight, length/height, BMI centiles	X	X	X	X	X	X	X	X
Respiratory culture	c	c	c	c	c	c	c	c
Chest Imaging	c	c	c	c	c	c	c	X
MBW/LCI measurement								X
Spirometry								X
Educate about tobacco exposure avoidance	X	c	c	c	c	c	c	c

X = Do at this visit

C = Consider if clinically indicated

* = At each meeting with family, consider whether the CRMS/CFSPID designation is still appropriate (is there evidence to transfer to a CF diagnosis?).

** = Review evidence from Year 6 assessment and discuss future care plans with the family.

sweat testing at 2 years of age is most discriminatory [29]. A normal FE-1 ($\geq 200 \mu\text{g/g}$) in the first year of life can fluctuate in infants with CF and it is appropriate to repeat this test at subsequent reviews if there is clinical concern (for example, persistent loose stools or failure to thrive) [45].

10.2.3. Evaluation and management themes over subsequent pre-school years (3–5 years)

- **Frequency of consultations:** Children with CRMS/CFSPID should be reviewed at least annually.
- **Sweat test:** further sweat tests may be undertaken annually if the specialist is concerned about clinical progress or the result at two years of age is intermediate. In the case of a sweat test result becoming positive (chloride $>59 \text{ mmol/L}$) in an asymptomatic child, we recommend that a repeat sweat test is undertaken. Ideally two consecutive positive results are required for this specific cohort of children to confirm the diagnosis, as they may be asymptomatic and have a previous inconclusive diagnosis.
- **CFTR variants:** the clinical relevance of *CFTR* variants should be checked every year as new CF-causing variants are still being characterised (*CFTR*-2 and *CFTR*-France are the most reliable resources for genotype/phenotype characterisation currently).
- **Respiratory culture:** A respiratory culture should be performed when clinically indicated (increased, persistent or productive cough). There is no evidence to support routine respiratory culture in well infants and this may lead to unnecessary medicalisation. For infants with a positive respiratory culture there is no evidence to guide management, for example, the use of antibiotics or the implementation of eradication protocols for *Pseudomonas aeruginosa*.
- **Chest imaging:** There is no evidence to support routine imaging in the early years of life in well infants, but it may be appropriate if there are clinical concerns.
- **Lung function:** Lung function measurement is not routinely undertaken in pre-school children although multiple breath

washout tests to measure lung clearance index (LCI) are increasingly available in this age group. There is no evidence to support routine measurement of LCI for infants with CRMS/CFSPID in the first five years, but if there are clinical concerns this may be appropriate, and if increased may support a clinical diagnosis of CF. Infants with CRMS/CFSPID did not have raised LCI compared to healthy controls in a study in California [46].

- **Genetic counselling:** Should be discussed if new knowledge of *CFTR* variants emerges.
- **Primary Care Physician:** should receive an annual report.
- **Information:** new information (change in sweat chloride values or updated classification of *CFTR* variants, etc.) should be discussed with the family. It is important that information is consistent and families do not receive mixed messages from different members of the CF team. Reinforcing messages from previous years is recommended.
- **Database:** children with a CRMS/CFSPID designation should be included on a national database, if available and consent is given. It is not appropriate for these children to be included on a CF registry, unless flagged as a CRMS/CFSPID designation.

10.2.4. Evaluation of the child at 6 years of age

At six years of age we propose that CRMS/CFSPID children have a more extensive evaluation as part of an assessment of progress and to inform plans for future management in partnership with the family. The 6 years of age assessment should include standard clinical evaluation and the following additional tests,

- Sweat test (sweat chloride measurement).
- A measure of respiratory function (multiple breath washout to measure lung clearance index (LCI) if possible and spirometry).
- Chest imaging: a limited high-resolution computerised tomogram (CT) without sedation may be undertaken with inspiratory and expiratory images, but this requires discussion of the benefits and risks. A chest radiograph may be an alternative, if CT is not available or not accepted by the parents, but may be

insensitive to subtle airways disease. In centres with expertise, a Magnetic Resonance (MR) scan may be undertaken. More evidence is required to establish the utility of imaging in this age group. The suggestions above reflect the reassuring results obtained from the French prospective study [30].

- Consider stool sample for FE-1 measurement (an isolated low FE-1 level should be interpreted with caution).

These results and the progress of the child should be discussed with the parents and a shared decision made on future management and follow-up plans. Information from this assessment may result in a CF diagnosis, but it is more likely to be reassuring and support rationalisation of care (see options below). The data from the prospective French study demonstrate that a significant proportion of asymptomatic CRMS/CFSPID children reach 6 years of age in good health with normal growth, lung function and imaging and normal sweat chloride values (<30 mmol/L). [30] It is unlikely that these children will convert to a diagnosis of CF.

There are three main options for further care after the assessment at 6 years of age:

- 1) Discharge from CF specialist care, with follow-up in primary care by their primary care physician.
- 2) Discharge from CF specialist care, but a further isolated specialist review as the child reaches adolescence (at the age of around 14–16 years, see below). This option gives the opportunity for more direct engagement with the young person.
- 3) Continue regular specialist review under the CRMS/CFSPID designation, either as part of the CF clinic or in a separate clinic (could be undertaken ‘virtually’ for example as an annual telephone call or video consultation).

Parents and the primary care physician should be informed that they should seek advice if the child develops any prolonged respiratory or abdominal symptoms (especially persistent loose stool, weight loss and pain). Parents should be well informed about the fact that such symptoms can also occur in adolescence or adulthood. In addition, parents should be informed that CFTR-RDs are possible later in life. This includes the issue of male infertility and why further assessment (semen analysis or ultrasonography of the vas deferens) may be appropriate in early adulthood.

10.2.5. The content of the adolescent review

Although a CRMS/CFSPID child carrying a VVCC and a CF-causing variant may well not develop any sign of disease by the age of six, this genotype, in association with an elevated IRT at birth, is a significant risk factor for the occurrence of some degree of clinical manifestations later in life.

A clinic review with the young person with a previous CRMS/CFSPID designation when they reach young adult age enables the physician to directly communicate the implications of the CRMS/CFSPID result for the individual. In addition, the physician can undertake a review of clinical progress and assessment of well-being at that point, reinforcing messages of healthy lifestyle, avoiding smoking and remaining active.

The consultation may be with the individual alone or together with the family, depending on their wishes and delivered in a sensitive manner. Parents should appreciate that topics around CFTR-RD, especially CBAVD, will be discussed at this visit, as they may want to raise these issues with their offspring before the consultation. The parents may not consider this an appropriate time for the consultation, which should then be postponed.

It may be up to ten years since the Year 6 consultation and some consideration of mechanisms to ensure that this happens after such a long gap between appointments is needed. As well as verbal information, the young person should be provided with written resources and other reliable information resources, as well as an email contact if they have questions in the future (Fig. 1).

It is imperative that the information from this consultation is recorded and provided for the young person and the primary care physician, as they will be the principal port-of-call for the young person as they continue their life.

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