

Cystic Fibrosis Foundation Practice Guidelines for the Management of Infants with Cystic Fibrosis Transmembrane Conductance Regulator-Related Metabolic Syndrome during the First Two Years of Life and Beyond

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Through early detection, newborn screening (NBS)¹ for cystic fibrosis (CF) offers the opportunity for early intervention and improved outcomes. NBS programs screen for hypertrypsinogenemia, and most also identify mutations in the CF transmembrane conductance regulator (CFTR) gene. Individuals identified by NBS are diagnosed with CF if they have an elevated sweat chloride level or if they have inherited 2 disease-causing mutations in the CFTR gene. Mutations in the CFTR gene can cause CF, but not all CFTR mutations are disease-causing. The term *CFTR-related metabolic syndrome* (CRMS) is proposed to describe infants identified by hypertrypsinogenemia on NBS who have sweat chloride values <60 mmol/L and up to 2 CFTR mutations, at least 1 of which is not clearly categorized as a “CF-causing mutation,” thus they do not meet CF Foundation guidelines for the diagnosis of CF. With what is now near-universal CF NBS in the United States, an increasing number of infants with CRMS are being identified. Given our inadequate knowledge of the natural history of CRMS, standards for diagnosis, monitoring, and treatment are absent. This document aims to help guide the monitoring and care of individuals with CRMS while our knowledge base on appropriate management evolves. (*J Pediatr* 2009;155:S106-16).

The Cystic Fibrosis Foundation convened a group of experts in July 2007 to create guidelines for the management of infants with CF, many of whom are detected through newborn screening (NBS).² NBS identifies infants at risk for CF by screening for hypertrypsinogenemia. Next, by the algorithm adopted in most US states, the CF transmembrane conductance regulator (CFTR) gene is interrogated for mutations, or, in other states, a second blood sample is analyzed for trypsinogen. Infants identified by NBS are diagnosed with CF if they have an elevated sweat chloride value or if they have inherited 2 disease-causing mutations in the CFTR gene. However, sweat chloride values are not always clearly in the diagnostic range, and not all CFTR mutations cause CF.³ Infants who do not have a diagnostic sweat chloride value \geq 60 mmol/L or 2 CF-causing mutations present the clinician and family with a diagnostic dilemma. Older individuals in these categories have been characterized as “atypical CF,” “non-classical CF,” “CFTR-related disorders,” “low-risk genotype,” or “mild variant CF,” but they present for diagnostic evaluation because of signs or symptoms, whereas infants identified by CF NBS are symptom free. For infants identified by CF NBS programs in whom CF cannot be diagnosed or clearly ruled out, we propose the designation *CFTR-related metabolic syndrome* (CRMS) to provide a clear name to families that (1) does not imply that the infant has CF; (2) includes patients with mutations that are of unproven or uncertain clinical relevance in addition to those associated with CFTR-related disorder⁴ (Table 1); and (3) can be associated with an International Classification of Disease code (277.9; unspecified disorder of metabolism in ICD-9; E88.9; Metabolic disorder, unspecified in ICD-10).

What follows is based on a systematic consensus of opinions from experts. These suggestions should be taken in the context of a rapidly expanding evidence base. In some patients, signs and symptoms may ultimately lead to a diagnosis of CF. Others will have development of symptomatic CFTR-related disorders such as pancreatitis or male infertility. Still others will never have any symptoms develop. The central difficulty in writing these guidelines is that some clinicians hesitate to apply a medical label to symptom-free infants who may never have any symptoms. Others have experience with patients who have had significant symptoms develop, and these physicians are reluctant to miss an opportunity for preventive care. It is for this reason that the following monitoring and treatment guidelines have been developed.

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CRMS	CFTR-related metabolic syndrome
NBS	Newborn screening
PCP	Primary care provider
PS	Pancreatic sufficient
RSV	Respiratory syncytial virus
TG	Thymidine-guanine

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Table I. Examples of CFTR mutations with regard to their clinical consequences (sorted by first number or letter, not in order of allele frequency)

Group A	May be Group A or Group B	Group B	May be Group B or Group C	Group C	Group D
“CF-Causing”		“CFTR-Related Disorders”		“No known Clinical Consequences”	“Unknown or Uncertain Significance”
1078delT	711+3A>G	L997F	TG11-T5	2752-15G/C	Many missense mutations*
1677delTA	D1152H	M952I		875+40A/G	
1717-1G>A	D565G	R668C-G576A-D443Y		E528E	
1898+1G>A	L206W	R74W-D1270N		F508C	
2184delA	R117H-T5			I148T	
2184insA	R117H-T7			I506V	
2789+5G>A	R297Q			I521F	
3120+1G>A	TG12-T5			I807M	
3659delC	TG13-T5			M470V	
3849+10kbC>T				P1290P	
621+1G>T				R75Q	
711+1G>T				T854T	
A455E					
E822X					
F508del					
G542X					
G551D					
G85E					
I507del					
N1303K					
R1158X					
R1162X					
R334W					
R347P					
R553X					
R560T					
S549N					
TG13-T5					
W1282X					

Adapted from Castellani et al.³ Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice, Journal of Cystic Fibrosis, May 2008. © 2008 European Cystic Fibrosis Society. Published by Elsevier B.V. with permission.

Note that this list does not include all CF-causing mutations seen in U.S. populations; some of these are more common in African-Americans and Hispanics.

*Certain common sequence (missense) variants with subclinical molecular consequences (eg, M470 V) may cosegregate on the same chromosome and exert a more potent, cumulative phenotypic effect.

Methods

The Delphi method was used prospectively and formally to determine consensus or lack thereof with the proposed recommendations.⁵ The CF Foundation charged a small working group with creating a general framework for monitoring and management of CRMS. Proposed care statements were circulated to a larger panel of 18 experts, which included representatives from the infant care guidelines group² and the CF Center Directors in Massachusetts, a state with 5 CF care centers and 9 years of experience with CF NBS (see designated participants listed at the end of the manuscript). Participants rated their agreement with each statement on a scale of 0 to 9 (0 = complete disagreement, 9 = complete agreement) and were given an opportunity to suggest rewording or present an argument or literature in support of the score. The responses were tabulated: values between 7 and 9 were considered good agreement; consensus was defined as $\geq 80\%$ participants in good agreement.

Statements were revised and recirculated for a second round of input from the experts. Some statements directly contradicted each other in the initial round of statements. These were dropped in round 2 if an opposing statement achieved consensus in round 1. Statements with $< 80\%$ agreement were reworded for round 2 on the basis of round 1 comments.

In round 2, the initial statements were sent out to the working group with a summary of round 1 tabulated scores (including mean, median and range, and summarized comments), and new or revised statements were redistributed to participants for repeat rating (Table II). Round 2 statements for which there was consensus are listed throughout the text at the end of each relevant section.

A draft of the guidelines was posted on a secure website for comment from CF Center care teams (physicians and ancillary care providers) and was revised as appropriate. Wording for 3 recommendations was modified in a manner that clarified the recommendation but did not change the meaning of the original statement for which consensus was achieved (Table II).

Diagnosing CFTR-Related Metabolic Syndrome

Unlike the presentation of older individuals with CFTR-related disorders, infants with CRMS do not have symptoms when they are identified through NBS. The CF Foundation Consensus Report on Guidelines for Diagnosis of CF describes the early diagnostic process.³ In most cases, infants found to have hypertrypsinogenemia on NBS undergo an initial sweat test by 2 to 4 weeks of age at an accredited laboratory, and most will also have had some CFTR mutation testing as part of the NBS. It is recommended that infants with initial sweat chloride values in the intermediate range

(30-59 mmol/L) have a repeat sweat test by 2 months of age, which may confirm the intermediate value or demonstrate resolution into the normal (<30 mmol/L) or abnormal (≥ 60 mmol/L) range. Infants with a persistently intermediate sweat chloride concentration should undergo in-depth CFTR DNA analysis, have access to genetic counseling, and have an evaluation by a CF specialist. These infants should undergo a third sweat test at approximately 6 months of age and be monitored by their primary care provider (PCP) and a CF clinician. Repeated sweat tests between 2 and 6 months of age may not add useful information. Thus, as described in **Figure 1** and **Table I**, after complete assessment, healthy infants with hypertrypsinogenemia should be considered to have CRMS if they have either: (1) intermediate sweat chloride concentrations on at least 2 occasions and fewer than 2 CF-causing CFTR mutations (Group A, **Table I**); or (2) a normal sweat chloride and 2 CFTR mutations, of which no more than 1 is known to be CF-causing (Group A, **Table I**) Infants with CRMS should be monitored because they are at increased risk for development of CF-like symptoms and because in some individuals, evolving signs and symptoms, new information about disease-causing CFTR mutations, or change in sweat chloride concentrations may ultimately lead to a diagnosis of CF.

Discussing the Implications of a CFTR-Related Metabolic Syndrome

It can be very difficult to explain the implications of CRMS to families who have a healthy-appearing infant. Extensive mutation analysis can define a diagnosis, but it also can be confounding when rare or complex alleles are found. Some examples are as follow:

CFTR Mutations with Variable Penetrance. Up to 7% of infants screened with a trypsinogen/DNA multmutation algorithm in which 2 mutations are identified will have 1 CF-causing mutation and R117H-T7.⁶ Some individuals with a CF-causing mutation on 1 allele and R117H associated with the T7 intron-8 polythymidine sequence on the other allele may have development of CF-like symptoms (although symptoms are rarely seen in early childhood and may not develop until adulthood.^{7,8} Others will not develop symptoms.^{9,10} Some CFTR mutations, including D1152H, have widely variable phenotypes.¹¹ If mutations such as D1152H are found in *trans* with other phenotypically variable CFTR mutations, such as R117H-T7, an already confounded picture becomes more complicated. Mutations such as D1152H and R117H, when compound heterozygous with a disease-causing CFTR mutation may lead to isolated symptoms later in life, such as pancreatitis.¹²

Intronic Mutations that Affect Splicing Efficiency.

The T5 intron-8 polythymidine sequence allele may result in an abnormal phenotype if it is in *trans* with a CF-causing mutation such as F508del.¹³ Analysis for thymidine-guanine (TG) repeat number adjacent to T5 may influence penetrance.¹⁴ When a TG12-T5 or TG13-T5 allele is found in *trans* to a CF-causing

mutation, it may result in CFTR-related disorder such as absence of the vas deferens or idiopathic pancreatitis, or may even lead to lung disease consistent with a diagnosis of CF.¹³

Non-CFTR Mutations that Affect Sweat Chloride.

Non-CFTR genes may cause increased sweat chloride, for example, mutations in the sodium channel ENaC (SCNN1B), and the interaction of these mutations with CFTR could potentially lead to bronchiectasis.¹⁵

CFTR Sequence Variants with Unknown or Uncertain Clinical Relevance.

Many “private” or rarely identified sequence variants that lead to missense mutations are of unknown or uncertain clinical significance but possibly could act either as a clinically significant mutation when found in *trans* to a disease-causing CFTR mutation or could have additive effects when found in *cis* with other mutations that have not been proven to cause disease.

These scenarios reinforce the fact that it is difficult to predict outcomes on the basis of genotype; however, physicians need to be informed and prepared to discuss these difficult issues with families. The authors of the Consensus on Use and Interpretation of CF Mutation Analysis in Clinical Practice recognized these limitations of genetic diagnosis and stated that phenotype is more important than genotype.⁴ **Table III** lists the most important issues to be discussed with the family at the time of initial discussion of the diagnosis. Family-friendly teaching material is provided in the **Appendix**. Symptoms are listed that should prompt the family to visit their PCP. A genetic counselor should be present at the discussion of CRMS, if possible, and should be available to the family in the future.

- The CF Foundation recommends that for individuals with CRMS, a genetic counselor should be present, if possible, in the discussion of genetic findings (83% agreement).

Coordination of Care with PCPs

The initial CF specialist assessment. Families will be making more visits to their PCP than to a CF specialist during the first 2 years of life, especially during the first 6 months of life when the family may be awaiting genetic testing results and the infant is not old enough for a third sweat test. The CF specialist should communicate directly with the PCP to explain the implications of CRMS immediately after the initial assessment. The PCP should contact the CF specialist if an infant with CRMS is not gaining weight, has loose stools or flatus, has abdominal pain, or has respiratory symptoms such as coughing or wheezing that do not resolve in 2 weeks. Open communication with the CF specialist is important if there are concerning findings at any time, especially if they are severe or if they progress rapidly. The management of infants with CRMS relies on collaborative decision making among the family, the PCP and the CF specialist, and the role of the PCP is crucial, especially if there are geographic, financial, or other barriers to follow-up at the CF Center.

Table II. Delphi questions and level of consensus

Statement number	Statement
1	A genetic counselor should be present, if possible, in the discussion of genetic findings in individuals with CRMS.
2	The CF Specialist should communicate directly with the primary care provider to explain the implications of CRMS.
3	The PCP should contact the CF specialist if an individual with CRMS is not gaining weight, has loose stools or flatus, has abdominal pain or has respiratory symptoms such as coughing or wheezing that do not resolve in 2 weeks.
4	A clinical assessment by a CF specialist should be performed by 2 months of age.
5	To prevent possible cross-infection, infants with CRMS should be assessed in a clinic adherent to CF Foundation guidelines for CF patients or in a clinic area separate from CF patients as local conditions allow.
6	CF Center ancillary personnel may need to see individuals with CRMS; this can be scheduled on an as-needed basis.
7	The following should be done at the time of the initial assessment: comprehensive history and physical including accurate weight and height measurements, an objective measure of pancreatic function such as fecal elastase, and an oropharyngeal culture. (Note: "fecal elastase" added to echo Infant Care Guidelines)
8	In a individual with CRMS a chest x-ray should be done if respiratory symptoms are present.
9	<i>The following laboratory tests may be done at the time of the initial assessment of an individual with CRMS if they have not been done recently: complete blood count with differential.</i>
10	<i>The following laboratory tests may be considered at the time of the initial assessment of an individual with CRMS if they have not been done recently: Liver function tests (AST, ALT, GGT, bilirubin).</i>
11	<i>The following laboratory tests may be considered at the time of the initial assessment of an individual with CRMS if they have not been done recently: albumin.</i>
12	<i>The following laboratory tests may be considered at the time of the initial assessment of an individual with CRMS if they have not been done recently: vitamin A and E levels.</i>
13	Patients should be treated per CF protocol if <i>Pseudomonas</i> is found on oropharyngeal swab, even if a definitive diagnosis of CF has not been established. (Note: wording changed from "should" to "may" on the basis of comments from public posting)
14	Symptom-free individuals with CRMS should be seen at least twice during the first year of life and once a year thereafter. Some symptom-free individuals may need more visits, depending on the comfort level of the family.
15	Oropharyngeal cultures processed as CF sputum should be obtained at every visit. (Note: "processed as CF sputum" added for clarification)
16	<i>1/8 tsp table salt per day may be considered for individuals with CRMS who have sweat chloride levels at the higher end of the intermediate range.</i>
17	Multivitamins designed for people who have CF should be prescribed to individuals with CRMS if there is laboratory evidence of vitamin A or vitamin E deficiency. (Note: recommendation expanded to include the need for evaluation of malabsorption if vitamin deficiency is noted based on comments from public posting)
18	In the absence of clinical or radiologic evidence of lung disease, routine airway clearance therapy should not be prescribed for individuals with CRMS.
19	Individuals with CRMS should not be exposed to cigarette smoke.
20	Individuals with CRMS should receive yearly influenza vaccine.
21	Pancreatic sufficient individuals with poor weight gain, loose stools, excessive flatus, or abdominal pain should have an objective measure of pancreatic functional status such as fecal elastase re-checked to rule out conversion to pancreatic insufficiency. (Note: "fecal elastase" added to echo Infant Care Guidelines)
22	Abdominal radiography should be considered in pancreatic-sufficient individuals with CRMS with poor weight gain, loose stools, excessive flatus, or abdominal pain to rule out constipation.
23	Airway clearance therapy may be considered if individuals with CRMS have recurrent or prolonged respiratory symptoms or have chest radiography findings suggestive of lower airway disease.

Agreement levels for the first 2 rounds*

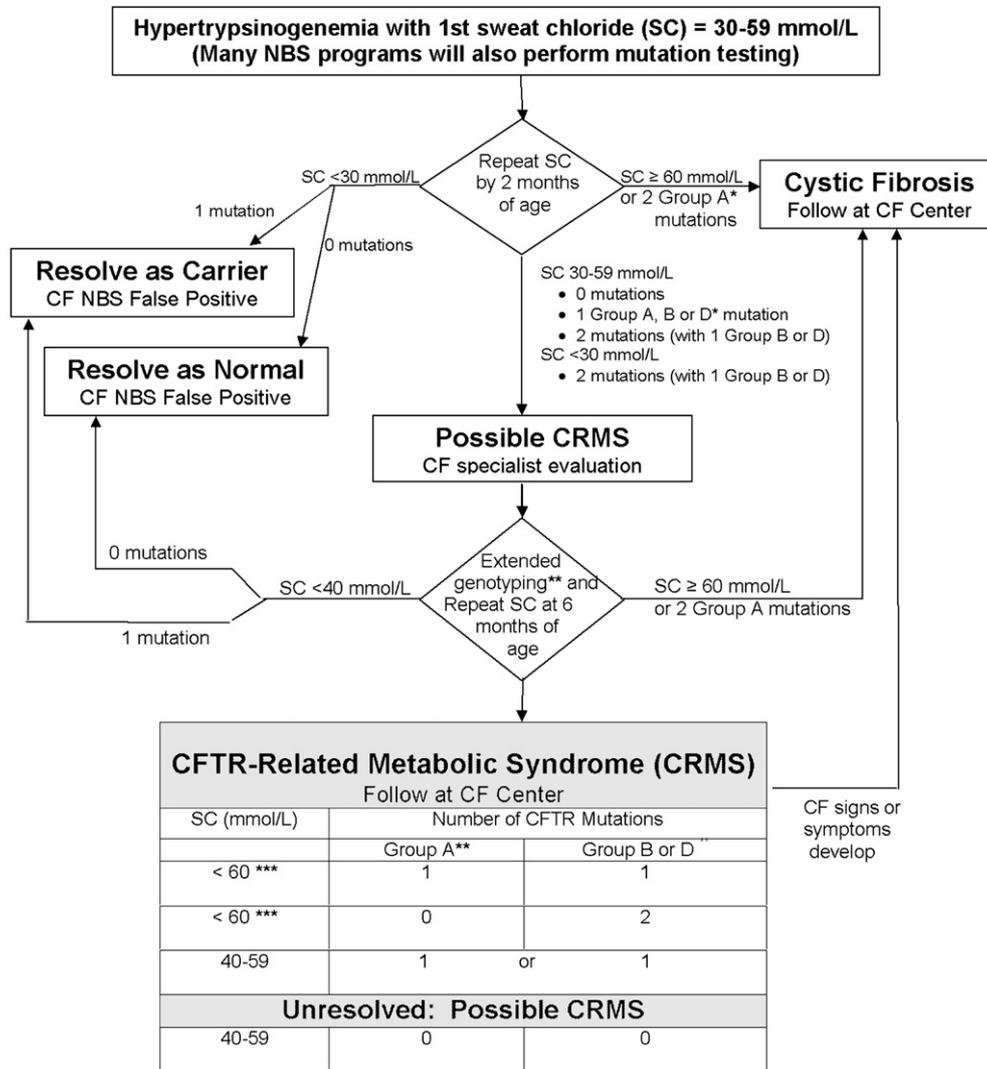
Statement number	Round 1			Round 2				
	Consensus (%)	Scores between 7 and 9	Range	Mean (median)	Consensus (%)	Scores between 7 and 9	Range	Mean (median)
1	66		1-9	7 (7)	83		4-9	8 (9)
2	94		4-9	9 (9)				
3	89 [†]		4-9	9 (9)	94		6-9	9 (9)
4	94		1-9					
5	83		4-9	8 (9)				
6	100		7-9	8 (9)				
7	94		6-9	9 (9)				
8	61 [‡]		1-9	7 (8)	94		6-9	9 (9)
9	78		3-9	8 (9)	76		5-9	7 (8)
10	78		0-9	7 (8)	65		0-9	7 (7)
11	72		3-9	7 (8)	76		0-9	8 (8)
12	78		1-9	7 (8)	76		0-9	8 (8)
13	83		2-9	8 (9)				
14	50		0-9	5 (6)	94		5-9	8 (8)
15	94		6-9	8 (9)				
16	67 [‡]		0-9	7 (8)	70		0-9	7 (8)
17	72 [‡]		2-9	7 (8)	94		6-9	8 (9)
18	78 [‡]		3-8	7 (8)	94		5-9	8 (9)
19	100		9	9 (9)				
20	94		6-9	9 (9)				
21	100		7-9	9 (9)				
22	61		0-9	7 (8)	82		3-9	8 (9)
23	50		1-9	6 (6)	88		4-9	9 (9)

Italicized statements never reached the level of consensus to become recommendations.

*The wording of some questions was modified between rounds 1 and 2 on the basis of feedback from the participants; a second round was not done if >80% consensus was achieved on round 1 and if there was not a significant change in wording.

†In this question, the interval for intervention was changed from 1 week to 2 weeks between round 1 and round 2.

‡For these questions, the wording changed from round 1 to round 2 to emphasize intervention if patients had symptoms or had a test result that informed the action.



* A= CF-causing, B= CFTR-related disorder, D= unknown or uncertain clinical relevance (3)
 ** Multimutation method, gene scanning or sequencing, duplication and deletion testing and evaluation for IVS-8 TG repeats; consider family evaluation for phasing to confirm mutations are *trans* (28).
 *** A lower limit for sweat chloride has not been defined

Figure 1. Identification of infants with of CFTR-related metabolic syndrome.

These principles continue to be true throughout the individual’s entire life, as symptoms may not develop until after the first few years of life. Key issues for PCPs are listed in **Table IV**.

- The CF Foundation recommends that for individuals with CRMS, the CF specialist should communicate directly with the PCP to explain the implications of CRMS (94% agreement).
- The CF Foundation recommends that for individuals with CRMS, the PCP should contact the CF specialist if the infant is not gaining weight, has loose stools or flatus, has abdominal pain, or has respiratory symptoms such as coughing or wheezing that do not resolve in 2 weeks (94% agreement).

Clinical Care

In patients with a definitive CF diagnosis, clinical manifestations can occur in the first few weeks of life.^{16,17} Although much less likely, early symptoms have also been reported in infants with CRMS.⁹ An infant with CRMS should have a clinical assessment by a CF specialist by no later than 2 months of age to allay anxiety and to establish a baseline evaluation. To prevent possible cross-infection, infants with CRMS should be assessed in a clinic adherent to CF Foundation guidelines for patients with CF¹⁸ or in a clinic area separate from patients with CF as local conditions allow. Care may be provided by a CF specialist alone, outside the context of a full CF team. The CF Center nurse or social worker may need to be involved to respond to telephone contacts or

Table III. Medical issues to discuss with the family at the time of identification of CFTR-related metabolic syndrome

- Assess emotional and educational status of the family
- Explain basic genetic concepts
 - Be sure that formal genetic counseling has been provided or is scheduled
- Provide a general description of CF symptoms and what causes them
 - Explain that there is a lot of incorrect and outdated information about CF (eg, from friends and family, in books, and on the web)
 - Explain why we think the infant likely does not have CF
 - Explain how we know the infant has CRMS
 - What was the process that led to this diagnosis
 - What does it mean if a child has CRMS
- Convey the news that we are uncertain about the prognosis:
 - We expect this child to lead a full life
 - Some, but not all individuals with CRMS may develop symptoms that should be treated
 - Some individuals with CRMS are at high risk for male infertility
 - This is why we need to establish the current baseline and follow this child in our clinic
 - We may not have all the answers right now, but new information becomes available all the time
- If individuals with CRMS cannot be seen separately from patients with CF, discuss infection control
- Describe the monitoring plan, how to contact the CF Care Center with questions or concerns; schedule the next visit before the family leaves

families who are having difficulty coping with the uncertainty of diagnosis. Other members of the CF care team do not need to see every individual with CRMS; this can be scheduled on an as-needed basis. Care by the full CF team may have the unintended consequence of reinforcing that the infant has CF, when in fact that is not the diagnosis.

- The CF Foundation recommends that for individuals with CRMS, a clinical assessment by a CF specialist should be performed by 2 months of age (94% agreement)
- The CF Foundation recommends that, to prevent possible cross-infection, infants with CRMS should be assessed in a clinic adherent to CF Foundation guidelines for patients with CF, or in a clinic area separate from patients with CF as local conditions allow (83% agreement)
- The CF Foundation recommends that for individuals with CRMS, CF Center ancillary personnel may need to see individuals with CRMS; this can be scheduled on an as-needed basis (100% agreement)

Appendix. Family-friendly written explanation of CRMS (This teaching sheet may be reproduced without permission)

CFTR-Related Metabolic Syndrome (CRMS)

(CFTR stands for *Cystic Fibrosis Transmembrane Conductance Regulator protein*, which is the salt channel that the “CF gene” makes; see “What Causes CF”)

Your child has CFTR-related metabolic syndrome (CRMS). Your infant had a newborn screen test for cystic fibrosis that gave an intermediate result. Your child does not have cystic fibrosis, but there are several reasons why we want your child to have regular check-ups with a doctor who is a cystic fibrosis specialist.

What is CRMS?

We say that a child has CFTR-related metabolic syndrome (CRMS) when they have had a sweat test or a genetic test that gives an intermediate result. Sweat tests are used to make the diagnosis of cystic fibrosis (CF), a genetic (inherited) disease. CF causes thick mucus to get stuck in the breathing tubes or sinuses, the intestines and organs such as the pancreas that are connected to the intestines, or the reproductive tract. Your child does not have CF, but 1 of 2 things makes us say that he or she has CRMS:

- The amount of salt in your child’s sweat is higher than in most children, although it is not high enough for us to say that he or she has CF. This could mean that your child is at higher risk to have problems in the breathing tubes or sinuses, the intestines and organs such as the pancreas that are connected to the intestines, or the reproductive tract.
- Your child has 1 or 2 mutations in his or her CF genes that don’t cause CF but could mean that your child is at higher risk to have problems in the breathing tubes or sinuses, the intestines and organs such as the pancreas that are connected to the intestines, or the reproductive tract.

What causes cystic fibrosis?

To understand CRMS you need to know something about cystic fibrosis (CF). CF is a genetic (inherited) disease. Genes are what tells our body things like “you will have blue eyes” or “you will have curly hair.” Genes come in pairs. You get one from your mother and one from your father. When there is a change in the code in a gene, it’s called a *mutation*. Some mutations don’t cause any problems at all, but some can cause diseases such as CF. People with CF have a disease-causing mutation in each of their 2 CFTR genes, so they inherited 1 mutation from their mother and 1 mutation from their father.

What are the symptoms of cystic fibrosis?

The CFTR gene controls the salt channels in skin, and because they have mutations that cause disease, people with CF have very salty skin. The CF gene also controls the salt channels in parts of the body that are lined with tissues that are like skin—the breathing tubes and sinuses, the intestines and organs such as the pancreas that are connected to the intestines, and the reproductive tract. People with CF get thick and sticky mucus in these parts of the body. The breathing tubes get clogged with thick mucus, and often people get a germ called *Pseudomonas* (pronounced “soo-dah-MOAN-us”). When we find *Pseudomonas*, we treat it because people who have this germ can have worse lung function. People with CF can get very serious and permanent lung problems.

What are the symptoms of CRMS?

We cannot clearly predict the future health of your child, although he or she is likely to remain healthy. Some people with CRMS have had development of problems in the breathing tubes or sinuses, the intestines and organs such as the pancreas that are connected to the intestines, or the reproductive tract, but we don’t know how many people with CRMS do not develop these problems. We believe that the best thing to do is for your child to have regular check-ups with a CF specialist so that we can find and treat any early changes if they happen.

You should see your regular doctor and possibly your CF specialist if your child

- is not gaining weight
- has loose stools, very bad gassiness, or constipation that lasts more than 2 weeks
- has very bad stomach aches
- has coughing or wheezing that lasts more than 2 weeks

If your CF specialist sees your child in an office where there are people with CF, they may take special precautions to be sure that your child is not exposed to the germ called *Pseudomonas*. It is important to know that *Pseudomonas* is everywhere, and even healthy babies might have *Pseudomonas*.

What can we do to keep our child healthy?

As is true for all children, people with CRMS should not be exposed to cigarette smoke. All children who are over 6 months of age should receive a yearly influenza vaccine.

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Table IV. Issues about CFTR-related metabolic syndrome for primary care providers

- Phenotype is more important than genotype
 - Many infants with CRMS will continue to be healthy and will thrive
 - Males with CRMS may be at higher risk of infertility
- Early symptoms can be subtle; open communication with the CF specialist is important if there are concerning symptoms such as:
 - Lack of weight gain or unresolved acute weight loss
 - Persistent loose stools or excessive flatus
 - Abdominal pain
 - Coughing or wheezing
- Contact the CF specialist if these symptoms persist >2 weeks
- If individuals with CRMS develop symptoms they may benefit from current and new treatments
- The CF Center is a resource for:
 - Medical advice
 - Psychosocial support for families who have difficulty coping with the uncertainty of this diagnosis
 - Information about new developments as they become available

The following should be done at the time of the initial assessment: comprehensive history including family history, and physical examination including weight, length, and head circumference measurements, an objective measure of pancreatic function such as fecal elastase, and an oropharyngeal culture (processed as a CF culture). A chest x-ray film should be obtained only if respiratory symptoms are present. The expert panel was queried regarding whether the following laboratory tests may be considered at the time of the initial assessment: complete blood count, liver function tests, albumin, vitamin A and vitamin E levels; consensus was not achieved. A recent statement by the European Cystic Fibrosis Society Neonatal Screening Working Group¹⁹ suggests an extensive evaluation of infants in this category, and some CF Centers in the United States and Canada have specific diagnostic algorithms that include specialized testing such as nasal potential difference measurements to attempt to better classify infants with CRMS. More extensive testing such as infant pulmonary function testing, chest computed tomography scanning (CT), bronchoalveolar lavage, nasal potential difference measurements or rectal ion channel and potential difference measurements may be useful in some situations; routine use of these tests at all CF Centers is not recommended.

- The CF Foundation recommends that for individuals with CRMS, the following should be done at the time of the initial assessment: comprehensive history and physical including accurate weight and height measurements, an objective measure of pancreatic function such as fecal elastase, and an oropharyngeal culture (94% agreement)
- The CF Foundation recommends that for individuals with CRMS, a chest x-ray film should be obtained if respiratory symptoms are present (94% agreement)

Persistent infection of the airways with *Pseudomonas aeruginosa* has been considered to be one of the phenotypic features consistent with a diagnosis of CF.³ The appearance of

mucoïd *P aeruginosa* strains has been considered pathognomonic for CF. In 1 report, oropharyngeal swabs positive for *Pseudomonas sp.* were seen intermittently in most infants with an uncertain diagnosis,²⁰ although the authors do not report whether these were mucoïd or nonmucoïd strains. Nonmucoïd *P aeruginosa* can be seen in healthy infants. In 1 study, 5 cohorts of 20 healthy infants (ages 0, 3, 6, 9, and 12 months) had oropharyngeal swabs obtained.²¹ Nonmucoïd *P aeruginosa* grew in 1 infant in the 6-month cohort and 1 set of twin infants who were living in the same household in the 12-month cohort. Furthermore, respiratory syncytial virus (RSV) is a frequent cause of respiratory symptoms in infants, and RSV has been found to mediate *Pseudomonas sp.* binding to normal epithelial cells.²² However, the presence of *Pseudomonas sp.* in an infant with an elevated though not diagnostic sweat test result warrants concern, and treatment of patients per CF protocol may be considered if *P aeruginosa* is found on an oropharyngeal swab.² Although bronchoscopy should be performed in infants with CRMS only for a clear-cut clinical indication, the presence of *Pseudomonas sp.* in the lower respiratory tract would be strongly suggestive of CF. *Staphylococcus aureus* or *Haemophilus influenzae* are not treated routinely in patients with CF² and by inference should not be treated in asymptomatic individuals with CRMS.

- The CF Foundation recommends that individuals with CRMS may be treated per CF protocol if *P aeruginosa* is found on an oropharyngeal swab, even if a definitive diagnosis of CF has not been established (83% agreement)

Subsequent CF Specialist Assessments. The sweat chloride test should be repeated at 6 months of age. An increase in the sweat chloride value ≥ 60 mmol/L establishes a diagnosis of CF. A sweat chloride value <40 mmol/L after 6 months of age is generally not consistent with a diagnosis of CF, although it can occur.²³ Symptom-free infants with CRMS should be seen by a CF specialist at least twice during the first year of life and once a year thereafter (Figure 2). Some symptom-free infants may need more visits, depending on the comfort level of the family. Suboptimal weight gain or recurrent respiratory symptoms do not make the diagnosis of CF certain, but in these instances, more frequent follow-up in the context of a CF Center may be warranted. Oropharyngeal swabs that are processed in the same manner as CF sputum should be obtained at each visit.

- The CF Foundation recommends that individuals with CRMS who are symptom free should be seen at least twice during the first year of life and once a year thereafter. Some symptom-free individuals may need more visits, depending on the comfort level of the family (94% agreement)

X= do at this visit

C= consider

AGE AT VISIT → INTERVENTIONS ↓	By 2 months of age	6 months of age	Age 1 and 2 years	Annually
CARE ISSUES				
Discuss diagnosis of CFTR-related metabolic syndrome	X	C	C	C
Discuss diagnosis with PCP	X	C	C	C
Measure weight, length, OFC	X	X	X	X
Vital signs and physical examination	X	X	X	X
Influenza vaccine		X	X	X
DIAGNOSTIC TESTING				
Sweat test	X	X		
Fecal elastase ¹	X	C	C	C
Respiratory culture ²	X	X	X	X
Blood tests (see manuscript text)	C	C	C	C
Chest x-ray ³	C	C	C	C
Abdominal x-ray	C	C	C	C
Spirometry (by standard adult methods) ⁴				X
EDUCATION				
Infection Control	X	C	C	C
Tobacco smoke exposure avoidance	X	X	X	X
Genetic counseling	X	C	C	C

1. Repeat fecal elastase only if individuals are symptomatic
2. Treat patients per CF protocol if *Pseudomonas* positive; acknowledge that healthy infants can be intermittently *Pseudomonas* positive
3. Obtain x-rays only if patients are symptomatic
4. Start monitoring when individuals are old enough to perform standard spirometry

Figure 2. Management of symptom-free individuals with a diagnosis of CFTR-related metabolic syndrome.

- The CF Foundation recommends that for individuals with CRMS, oropharyngeal cultures processed as CF sputum should be obtained at every visit (94% agreement)

Initial Therapy. It is difficult to make definitive recommendations about preventive metabolic and nutritional therapies for symptom-free infants with CRMS. Infants with CF are at risk for salt depletion if they do not receive supplemental salt. Although the extent of salt loss is not likely to be as great in infants with CRMS as in infants with CF, the amount of salt in the sweat for those with sweat chloride values in the intermediate range is by definition greater than 3 standard deviations above the norm. Members of the expert panel were queried concerning salt supplementation for infants with CRMS, but consensus was not achieved. Patients with CF can be deficient in the fat-soluble vitamins A, E, D, and K. Individuals with CRMS are almost universally pancreatic sufficient (PS) and CF-PS patients are at low risk for vitamin deficiency. Members of the expert panel did not achieve con-

sensus on a recommendation to check fat-soluble vitamin levels. Some clinicians may choose to measure fat-soluble vitamin levels, and if levels are found to be low, the expert panel recommended supplementation with vitamins designed for patients with CF as opposed to standard multivitamins. Further diagnostic testing should be pursued to evaluate pancreatic, intestinal, or hepatic causes of malabsorption in patients with fat-soluble vitamin deficiency.

- Although the CF Foundation cannot recommend routine measurement of fat-soluble vitamin levels for individuals with CRMS, if laboratory evidence of a deficiency is documented, further evaluation for malabsorption is needed, and multivitamins designed for people with CF should be prescribed (94% agreement)

Because lung disease is the most serious manifestation of CF and has been described in individuals with CRMS, therapies to prevent lung disease were considered. The CF Foundation Evidence-Based Guidelines for Management of Infants with CF² states, "Evidence to support guidelines for early

prevention or treatment of pulmonary disease in infants with CF is sparse.” Because it is unclear whether infants with CRMS will ever have development of CF-like pulmonary complications, in the absence of clinical or radiologic evidence of lung disease, routine airway clearance therapy should not be prescribed. As for all children, individuals with CRMS should not be exposed to cigarette smoke. As per the recommendation of the American Academy of Pediatrics for all children, individuals with CRMS who are older than 6 months of age should receive an annual influenza vaccine, as well as all other routine immunizations. The question of whether to use palivizumab was not presented to the expert panel for consideration because infants with CRMS were not perceived to be at higher risk from RSV infection than the general population.

- The CF Foundation recommends that for individuals with CRMS, in the absence of clinical or radiologic evidence of lung disease, routine airway clearance therapy should not be prescribed (94% agreement)
- The CF Foundation recommends that individuals with CRMS should not be exposed to cigarette smoke (100% agreement)
- The CF Foundation recommends that individuals with CRMS should receive annual influenza vaccine (94% agreement)

Subsequent Therapy. Patients with CF who are PS have enough pancreatic enzyme secretion to prevent steatorrhea, but the amount of secretin-stimulated bicarbonate-rich pancreatic fluid is diminished.²⁴ Intermittent ductal obstruction puts these patients at risk for recurrent pancreatitis, and as a result some become pancreatic insufficient. Individuals with CRMS may have similar diminished pancreatic function. An objective measure of pancreatic functional status such as fecal elastase should be rechecked after the initial visit if there is poor weight gain, loose stools, excessive flatus, or abdominal pain. It should be noted that enteropathy can cause secondary pancreatic insufficiency and a low fecal elastase,^{25,26} thus infants with failure to thrive and low elastase should have the fecal elastase rechecked when their nutritional status improves. Patients with CF who are PS may have constipation as a result of loss of intraluminal fluid volume; constipation may contribute to a poor appetite and poor weight gain, which could be misinterpreted as resulting from a change from PS to pancreatic insufficient. Abdominal radiography should be considered in pancreatic-sufficient individuals with CRMS with poor weight gain, loose stools, excessive flatus, or abdominal pain to rule out constipation.

- The CF Foundation recommends that for individuals with CRMS, those who are PS and have poor weight gain, loose stools, excessive flatus, or abdominal pain should have an objective measure of pancreatic functional status such as fecal elastase rechecked to rule out conversion to pancreatic insufficiency (100% agreement)
- The CF Foundation recommends that for individuals with CRMS, abdominal radiography should be consid-

ered in those with poor weight gain, loose stools, excessive flatus, or abdominal pain to rule out constipation (82% agreement)

As noted above, some individuals may have development of respiratory complications whereas others will not. Viral illnesses are very common in infants and young children, so it may be difficult to determine if cough or other respiratory symptoms are within normal limits or related to the underlying CRMS. Individuals with cough that does not resolve after 2 weeks should be evaluated by their PCP (see recommendation in “Coordination with Primary Care Providers” section above). Airway clearance therapy may be considered if patients have recurrent or prolonged respiratory symptoms, or have chest x-ray findings suggestive of lower airway disease. These infants will likely need a more in-depth diagnostic evaluation and more frequent follow-up. Counseling for the avoidance of smoke exposure should be incorporated into CF specialist monitoring visits and should continue to be reinforced by the PCP (see recommendation in “Initial Therapy” section above).

- The CF Foundation recommends that for individuals with CRMS, airway clearance therapy may be considered if individuals have recurrent or prolonged respiratory symptoms or have chest x-ray findings suggestive of lower airway disease (88% agreement)

Because the genesis of this document was by a panel considering infant care, questions concerning male infertility were not presented to the expert panel for consideration. However, males with CRMS who have a genotype that includes the R117H mutation are likely to have absence of the vas deferens. The reproductive potential of males with CRMS with other mutations is unclear; however, many men with obstructive azoospermia have abnormalities in a range of CFTR exons or introns.^{27,28} Families need to be made aware of the potential for reproductive problems in males with CRMS, and at the appropriate age their sons should be offered testing to define their reproductive status. Physicians discussing CRMS should clarify that sexual function is normal and that artificial reproductive technologies such as microepididymal sperm aspiration and testicular sperm extraction may be able to aid in the fertility of patients found to have azoospermia.

Future Research. Clinicians need evidence to determine the optimal clinical management of individuals with CRMS. Gathering clinical and genetic information through a central reporting system such as the CF Foundation Patient Registry would be an important first step to help us learn more about CRMS. Ideally, the development of new biomarkers, as well as identification of genetic modifiers, may enable us to provide more accurate prognostic information to families. These markers could also help determine which individuals with CRMS are at highest risk for complications and merit closer surveillance.

Conclusion

When CF NBS identifies an infant with CRMS, a complex and potentially difficult situation is created for the family, CF specialist, and PCP. Care should be given to first, do no harm by creating a vulnerable child in the parents' eyes because many of these individuals will live a long and healthy life with a low risk for development of signs or symptoms of CF. However, because some will become symptomatic and preventive care is preferable to symptomatic care, these individuals should not be lost to specialist follow-up. Newer techniques for diagnosis and prognosis may become available and then could be offered to families. This document cannot encompass every situation and is meant to provide general recommendations rather than a set of rigid guidelines. Recommendations are likely to change as more evidence becomes available. By tracking the clinical outcomes of individuals with CRMS and with the development of new biomarkers, as well as identification of genetic modifiers, we hope to alleviate the anxiety and uncertainty caused by this ambiguous situation. ■

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