



# Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation

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**Objective** Cystic fibrosis (CF), caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, continues to present diagnostic challenges. Newborn screening and an evolving understanding of CF genetics have prompted a reconsideration of the diagnosis criteria.

**Study design** To improve diagnosis and achieve standardized definitions worldwide, the CF Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria and terminology for other disorders associated with *CFTR* mutations. An a priori threshold of  $\geq 80\%$  affirmative votes was required for acceptance of each recommendation statement.

**Results** After reviewing relevant literature, the committee convened to review evidence and cases. Following the conference, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of which needed revisions and a second round of voting.

**Conclusions** It is recommended that diagnoses associated with *CFTR* mutations in all individuals, from newborn to adult, be established by evaluation of CFTR function with a sweat chloride test. The latest mutation classifications annotated in the Clinical and Functional Translation of CFTR project (<http://www.cftr2.org/index.php>) should be used to aid in diagnosis. Newborns with a high immunoreactive trypsinogen level and inconclusive CFTR functional and genetic testing may be designated CFTR-related metabolic syndrome or CF screen positive, inconclusive diagnosis; these terms are now merged and equivalent, and CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis may be used. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes for use in diagnoses associated with *CFTR* mutations are included. (*J Pediatr* 2017;181S:S4-15).

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in the US, affecting approximately 1 in 4000 newborns in the US,<sup>1-3</sup> and occurring at higher frequencies in some European countries.<sup>4,5</sup> CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (*CFTR*), which encodes an ion channel protein,<sup>6</sup> with more than 2000 mutations identified to date (<http://www.genet.sickkids.on.ca/cftr/app><sup>7</sup>).

A diagnosis of CF initially relied on phenotype, with clinical recognition of characteristic signs and symptoms.<sup>8,9</sup> However, because of widespread CF newborn screening (NBS), at least 64% of new CF diagnoses in the US now occur in

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List of 2015 CF Foundation Diagnosis Consensus Conference Committee and Executive Subcommittee members is available at [www.jpeds.com](http://www.jpeds.com) (Appendix).

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CF	Cystic fibrosis
CFSPID	CF screen positive, inconclusive diagnosis
CFTR	CF transmembrane conductance regulator
CFTR2	Clinical and Functional Translation of CFTR
CRMS	CFTR-related metabolic syndrome
ECFS	European CF Society
ICD-10	<i>International Statistical Classification of Diseases and Related Health Problems, 10th Revision</i>
ICM	Intestinal current measurement
IRT	Immunoreactive trypsinogen
NBS	Newborn screening
NPD	Nasal potential difference

asymptomatic or minimally symptomatic infants following a positive NBS result.<sup>10</sup> Although the majority of infants who screen positive can be readily diagnosed with CF after a confirmatory test showing high sweat chloride concentration, the diagnosis is not clear in some individuals,<sup>11,12</sup> leading to persistent challenges<sup>13</sup> and stresses, including a potentially disturbed parent/child relationship.<sup>14-16</sup> Furthermore, universal NBS was implemented only recently in the US, and many individuals born prior to 2010 have not been screened. Diagnosis of CF in the nonscreened population can be challenging because the age of onset and severity of symptoms can differ greatly as a result of highly variable levels of CFTR dysfunction. Presenting manifestations can include pancreatitis, respiratory symptoms, chronic sinusitis, and male infertility.<sup>9,17-19</sup>

The last few years have seen significant growth of phenotypic and genotypic information on CF that can help with interpretation of the disease status in many patients. International collection of clinical data from individuals with CF<sup>20</sup> and laboratory advances<sup>21</sup> provide insight into the functional and physiological impact of the most common mutations.<sup>22</sup> Because of this new information, and to seek harmony with the diagnostic criteria and terminology<sup>23</sup> of the European CF Society (ECFS), it was decided that the 2008 diagnostic guidelines<sup>24</sup> of the CF Foundation should be revised.

The CF Foundation convened an international committee of experts in the diagnosis of CF to update diagnostic guidance and achieve standardization in definitions worldwide. The mission of this committee was to develop clear and actionable consensus guidelines on diagnosis of CF and other conditions associated with mutations in the *CFTR* gene such as CFTR-related metabolic syndrome (CRMS)<sup>25</sup> or CF screen positive, inconclusive diagnosis (CFSPID),<sup>26</sup> and CFTR-related disorders.<sup>27</sup> The recommendations in this article address individuals with both clear and unclear diagnoses, including infants with positive NBS (defined as any result other than normal) and/or prenatal diagnosis,<sup>28</sup> and individuals with CF-like symptoms who were either never screened or who had false negative newborn or prenatal screening results.<sup>9</sup> Case studies, designed to show how the recommendations should be applied in challenging clinical scenarios, can be found in additional articles published throughout this Supplement.<sup>9,28,29</sup>

## Methods

An international consensus committee was selected and tasked with the development of guidelines on the diagnosis of CF; 32 experts made up this committee. Committee selection was designed to include participants representative of worldwide CF care communities, particularly pediatric CF providers with NBS experience, and other relevant specialists, including adult CF providers. Before the consensus conference, the committee reviewed the existing CF Foundation diagnosis guidelines<sup>24</sup> and a list of publications on CF diagnosis published since the 2008 CF Foundation Diagnosis Guidelines, including 10 key articles selected by conference cochairs. The conference was held immediately prior to the North American CF Conference in October 2015.

At the consensus conference, committee members presented and discussed new studies and data on CF diagnosis. An executive subcommittee, consisting of 10 representatives from 4 countries, developed the consensus statements at subsequent meetings. These statements were reviewed by the entire consensus committee and voted on by the members using an electronic survey tool (SurveyMonkey, Palo Alto, California).<sup>30</sup> An a priori threshold of  $\geq 80\%$  affirmative votes was required for acceptance. Individuals voting against a statement were asked to provide a revised statement and/or explanation for their vote. Feedback on the statements that did not reach 80% agreement was reviewed by the committee cochairs, and those statements were revised with input from the rest of the executive subcommittee. The revised statements were then resubmitted for voting.

After the recommendation statements were agreed upon, they were presented to the ECFS at the Diagnostic Network Working Group annual meeting in February 2016 to help engage all parties in the discussion. The draft manuscript was distributed for feedback from the executive subcommittee, conference committee, the CF Foundation's CF Center Committee, all CF centers in the US, parents of screened infants, and a variety of international organizations and their members during a public comment period.

## Results

In the survey, participants were able to vote in agreement, disagreement, or to abstain. However, in each of the 2 surveys distributed for reviewing the consensus statements and voting, 1 committee member (a different person each time) did not respond. Thus, the 1 committee member who did not participate in the first voting exercise did not constitute an abstention. A vote was taken on 28 statements initially; 8 did not reach at least 80% agreement. The 8 statements that did not pass were reviewed and revised, and reduced to 7 statements by the chairs and the executive committee and sent out for a second round of voting. All but 1 member of the 32 committee members participated in this vote (ie, 1 was nonresponsive). All 7 of the revised statements passed the 80% threshold in the second round of voting.

The committee approved 27 consensus statements (**Table 1**) in 4 overlapping categories that apply to: (1) both screened and nonscreened populations; (2) newborn screened populations and fetuses undergoing prenatal testing; (3) infants with uncertain diagnosis and designated either CRMS or CFSPID (now considered to be the same); and (4) patients presenting clinically who represent nonscreened populations, including children born at home or in regions before NBS implementation, those with false negative screening tests, and older nonscreened individuals.

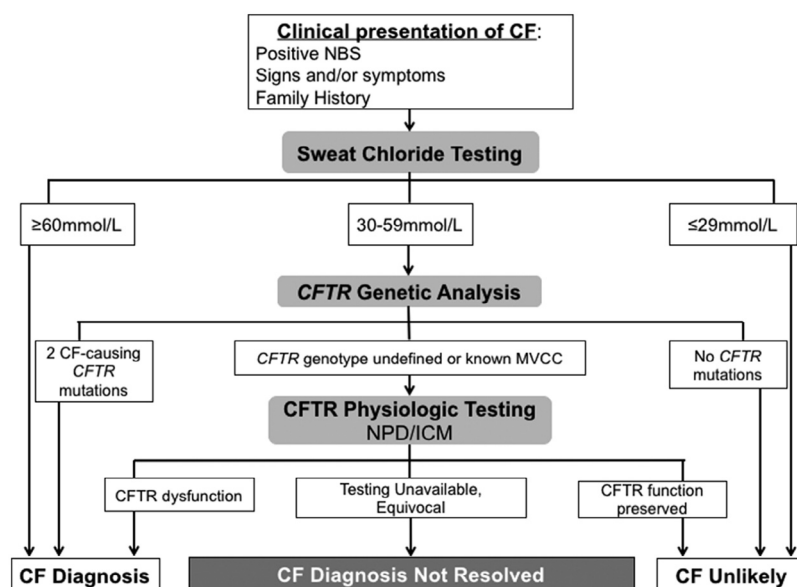
The **Figure** provides a simplified algorithm for how these consensus statements should be applied to individuals suspected of having CF because of a positive NBS result, the appearance of signs or symptoms, or recognition of immediate family history of CF (most often sibling, but may also include

**Table I. Consensus recommendations for diagnosis of CF\***

Statement numbers	Consensus statements	Vote	Abstain (n)
1	Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the CLSI 2009 Guidelines.	100%	0
2	Newborns with a positive CF newborn screen, to increase the likelihood of collecting an adequate sweat specimen, should have the test performed bilaterally and when the infant weighs >2 kg, and is at least 36 wk of corrected gestational age.	87%	0
3	Newborns greater than 36 wk gestation and >2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 d of age, ideally by the end of the neonatal period (4 wk of age).	93%	1
4	In infants with presumptive CF identified through NBS, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.	83%	1
5	Sweat chloride analysis should be performed within a few hours of sweat collection and the results and interpretations should be reported to clinicians and parents or patients, as soon as possible and certainly on the same day.	90%	0
6	In individuals presenting with a positive newborn screen, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made if the sweat chloride value is $\geq 60$ mmol/L.	93%	0
7	Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo <i>CFTR</i> genetic testing if the <i>CFTR</i> genotype was not available through the screening process or is incomplete.	100%	0
8	In individuals with a positive newborn screen, a sweat chloride <30 mmol/L indicates that CF is unlikely.	82%	2
9	Individuals with clinical features that may be consistent with CF who have a sweat chloride <30 mmol/L indicates that CF is less likely. It may, however, be considered if evolving clinical criteria and/or <i>CFTR</i> genotyping support CF and not an alternative diagnosis.	80%	0
10	Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on two separate occasions may have CF. They should be considered for extended <i>CFTR</i> gene analysis and/or <i>CFTR</i> functional analysis.	90%	0
11	The latest classifications identified in the CFTR2 project ( <a href="http://www.cftr2.org/index.php">http://www.cftr2.org/index.php</a> ) should be used to aid with CF diagnosis: <ul style="list-style-type: none"> <li>• CF-causing mutation: individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed)</li> <li>• Mutation of varying clinical consequence (MVCC): a mutation that in combination with a CF-causing mutation or another MVCC mutation may result in CF</li> <li>• Uncharacterized mutation/mutation of UNK: mutation that has not been evaluated by CFTR2 and may be disease causing or of variable clinical consequence or benign</li> <li>• Non-CF-causing mutation: individuals with 1 or more are unlikely to have CF (as a result of that allele)</li> </ul>	100%	0
12	In individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, the identification of 2 CF-causing mutations (defined by CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to confirm the diagnosis.	87%	0
13	The absence of detection of 2 CF-causing <i>CFTR</i> mutations does not exclude a diagnosis of CF.	93%	1
14	If further CF functional testing is needed (NPD and ICM), it should be performed in a validated reference center with trained staff certified by the CF Foundation TDN or ECFS Clinical Trial Network.	100%	0
15	In individuals with a positive newborn screen but variable or uncharacterized <i>CFTR</i> mutations (<2 CF-causing mutations), the diagnosis of CF can be made by demonstrating <i>CFTR</i> dysfunction (a sweat chloride $\geq 60$ mmol/L or CF-typical NPD or ICM).	93%	0
16	The term CRMS is used in the US for healthcare delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS.	96%	2
17	The term CRMS/CFSPID is reserved for individuals who screen positive without clinical features consistent with a diagnosis of CF.	83%	1
18	The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either: <ul style="list-style-type: none"> <li>• A sweat chloride value &lt;30 mmol/L and 2 <i>CFTR</i> mutations, at least 1 of which has unclear phenotypic consequences</li> <li>OR</li> <li>• An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations</li> </ul>	86%	1
19	Children designated as CRMS/CFSPID should undergo at least one repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center.	86%	1
20	Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms.	83%	1
21	Children designated as CRMS/CFSPID can be considered for extended <i>CFTR</i> gene analysis (sequencing and or deletion duplication testing), as well as <i>CFTR</i> functional analysis (NPD/ICM) testing to further define their likelihood of developing CF.	80%	0
22	The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of <i>CFTR</i> (sweat chloride, and possibly NPD/ICM), <i>CFTR</i> genetic analysis, and clinical assessment by the CF clinicians caring for the patient.	90%	0
23	Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies.	100%	1
24	Research Recommendation: Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow-up.	96%	0
25	For individuals presenting with CF symptoms, the same diagnostic criteria recommended for the screened population for sweat chloride testing, <i>CFTR</i> genetic analysis, and <i>CFTR</i> functional testing should be used to confirm a CF diagnosis.	93%	0
26	The diagnosis of <i>CFTR</i> -related disorder has been defined as a monosymptomatic clinical entity (CBAVD/pancreatitis/bronchiectasis) associated with <i>CFTR</i> dysfunction that does not fulfill the diagnostic criteria for CF.	86%	2
27	Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF, because these terms have no harmonized definition and could be confusing for families or caregivers.	83%	1

CBAVD, congenital bilateral absence of the vas deferens; CLSI, Clinical and Laboratory Standards Institute; CTN, Clinical Trial Network; ICM, intestinal current measurement; MVCC, mutation of varying clinical consequence; NPD, nasal potential difference; TDN, Therapeutics Development Network; UNK, unknown clinical consequence.

\*In each of the 2 surveys distributed for reviewing the consensus statements drafted and voting, 1 committee member, a different person each time, did not respond.



**Figure.** CF is diagnosed when an individual has both a clinical presentation of the disease and evidence of CFTR dysfunction. The tests of CFTR function are not always done in this order, but hierarchically to establish the diagnosis of CF, sweat chloride should be considered first, then *CFTR* genetic analysis, and then CFTR physiologic tests. All individuals diagnosed with CF should have a sweat test and a *CFTR* genetic analysis performed. Rare individuals with a sweat chloride <30 mmol/L may be considered to have CF if alternatives are excluded and the other confirmatory tests (genetic, physiologic testing) support CF. If only 1 *CFTR* variant is identified on limited analysis, further (“extended”) *CFTR* testing should be performed.<sup>22</sup> CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence (MVCC) mutations; CF is unlikely if only non-CF-causing mutations are found. If a CF diagnosis is not resolved, CRMS/CFSPID (following NBS) or CFTR-related disorder should be considered.<sup>9,29</sup> Rarely, no distinct label may be appropriate but further follow-up may be warranted. In these cases, the use of “CF carrier” or the specific clinical problem should be used for characterization/labeling purposes.

parent or child). It should be noted that a positive NBS result does not mean the infant has CF; the probability of a CF diagnosis following a positive result varies greatly depending on the NBS method used.

Even though many individuals enter this algorithm through a positive newborn screen in which *CFTR* genetic testing was done, the diagnosis of CF is primarily based on the direct demonstration of abnormal CFTR function by measurement of chloride concentration in the sweat.<sup>24</sup> Although obtaining an adequate sweat specimen for chloride measurements can be challenging, particularly in very young infants, experience and studies have shown that this is feasible in full-term infants during the first postnatal month (ie, during the neonatal period).<sup>31-34</sup> Following the committee’s recommendations will improve reliability of the sweat test result.

### Sweat Chloride Testing and Presumptive Diagnosis

(1) **All populations:** Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the *Clinical and Laboratory Standards Institute 2009 Guidelines*. Following appropriate protocols for performing the sweat test<sup>32</sup> is important for achieving accurate results and minimizing collection of inadequate amounts of sweat (quantity not sufficient).<sup>28,33-37</sup>

- (2) **For newborns:** Newborns with a positive CF newborn screen, to increase the likelihood of collecting an adequate sweat specimen, should have the test performed bilaterally and when the infant weighs >2 kg and is at least 36 weeks’ corrected gestational age. Sweat samples collected bilaterally must not be combined; instead, they should be analyzed separately, providing a useful quality control measure.<sup>33</sup>
- (3) **For newborns:** Newborns greater than 36 weeks’ gestation and >2 kg body weight with a positive CF newborn screen, or positive prenatal genetic test, should have sweat chloride testing performed as soon as possible after 10 days of age, ideally by the end of the neonatal period (4 weeks of age). For a variety of reasons related to efficient, effective follow-up and optimizing care, sweat chloride testing should occur as soon as possible when positive screening results are reported and can be as early as 48 hours after birth.<sup>33</sup> The committee recognizes that many NBS programs do not report results by this time and, therefore, recommends that sweat chloride testing proceed as soon as possible after results are available; generally, this is no later than 10 days of age. Although gestational age and weight must be considered,<sup>38</sup> testing should occur if at all possible before the end of the neonatal period because malnutrition and other risks such as potentially fatal hyponatremic dehydration may occur even in the first few weeks of life.<sup>39-42</sup>



- (4) **For newborns:** *In infants with presumptive CF identified through NBS, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.* Optimal outcomes depend on early intervention. Efforts to obtain adequate quantities of sweat and accurate sweat chloride values should not delay start of salt supplementation or other appropriate therapies.<sup>43</sup> The CF Foundation recommends that infants with CF have an initial visit at an accredited CF care center within 24-72 hours of diagnosis,<sup>43</sup> and timing of the initial visit for infants with a presumptive diagnosis should aim to meet this timeframe. A presumptive diagnosis of CF for purposes of treatment initiation can include the following clinical circumstances: (1) positive CF newborn screen showing 2 CF-causing *CFTR* mutations (see below); (2) positive CF newborn screen and clinical signs and symptoms of CF; and (3) meconium ileus, with or without a positive newborn screen.

However, definitive diagnosis requires demonstration of *CFTR* dysfunction. A date of presumptive diagnosis should be recorded to permit evaluation of timeliness of diagnosis and treatment within NBS programs. However, for purposes of providing standardized data to the CF Foundation Patient Registry, the date of the first positive sweat chloride test should be reported as the date of diagnosis.

- (5) **All populations:** *Sweat chloride analysis should be performed within a few hours of sweat collection, and the results and interpretations should be reported to clinicians and parents or patients, as soon as possible and certainly on the same day.* Prompt reporting should be made regardless of sweat test results to reduce family or patient stress.<sup>44-47</sup> A second, confirmatory, sweat test following an initial positive result is not necessary; this is a change from previous CF Foundation diagnostic guidelines.<sup>24,48</sup>

### Sweat Chloride Test Results $\geq 60$ mmol/L

- (6) **All populations:** *In individuals presenting with a positive newborn screen, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made if the sweat chloride value is  $\geq 60$  mmol/L.* Even though the sweat test is commonly used for diagnosis of individuals presenting with symptoms of CF, many newborns are reported as having CF based solely on a positive NBS result. However, NBS tests must always be considered as screening procedures and not diagnostic studies. The genetic analysis included as part of many NBS programs must not be relied upon for conclusive diagnosing and/or genotyping, as errors can arise from problems with Guthrie card labelling,<sup>49,50</sup> changes in the mutation panel used by the NBS program (eg, as described by Watson et al<sup>51</sup>), NBS laboratory errors including DNA misinterpretations, or detection of 2 *CFTR* mutations in *cis* (ie, on the same chromosome).<sup>22,52,53</sup> All of these problems have occurred and will occur again.
- (7) **For newborns:** *Individuals who screen positive and meet sweat chloride criteria for CF diagnosis should undergo *CFTR**

*genetic testing if the *CFTR* genotype was not available through the screening process or is incomplete.* Genetic testing is an important part of the diagnostic work-up, and it is not uncommon for a positive NBS result to include the recognition of 2 CF-causing mutations. Even in the presence of a positive sweat test, the identification of 2 CF-causing mutations should be confirmed in a clinical genetics laboratory capable of performing in-depth genetic analysis when required to further define CF risk (eg, the length of polyT tracts with the c.350G>A [legacy: R117H] *CFTR* mutation).<sup>54,55</sup> Confirmation of genetic testing results with an FDA-approved companion diagnostic test also has additional value in therapy selection<sup>56</sup> and access.<sup>57,58</sup>

### Sweat Chloride Test Results <30 mmol/L

- (8) **For newborns:** *In individuals with a positive newborn screen, a sweat chloride <30 mmol/L indicates that CF is unlikely.* Sweat chloride testing may be repeated if indicated by family history, or if symptoms suggestive of CF occur.
- (9) **All populations:** *Individuals with clinical features that may be consistent with CF who have a sweat chloride <30 mmol/L indicates that CF is less likely. It may, however, be considered if evolving clinical criteria and/or *CFTR* genotyping support CF and not an alternative diagnosis.* The level of sweat chloride below which CF is considered unlikely is 30 mmol/L for all age groups. This is a change from previous guidelines for individuals >6 months of age (the previous limit was 40 mmol/L) because patients have been definitively diagnosed with CF with chloride values in the 30-39 mmol/L range.

Details regarding the diagnosis of CF in the very rare individual with sweat chloride <30 mmol/L are published elsewhere.<sup>22</sup> Some *CFTR* mutations, such as c.3717 + 12191C>T (legacy: 3849 + 10 kb C- > T), are associated with low sweat chloride values; in these cases, an alternative diagnosis does not need to be ruled out.<sup>9,59,60</sup>

### Sweat Chloride Test Results of 30-59 mmol/L

- (10) **All populations:** *Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended *CFTR* gene analysis and/or *CFTR* functional analysis.* Individuals with sweat chloride concentrations in the intermediate range will need further study to establish or rule out a CF diagnosis.<sup>12,61-63</sup> Evidence may be provided by *CFTR* genotype<sup>20</sup> (an article in this Supplement provides a discussion of *CFTR* genetic testing and interpretation in detail<sup>22</sup>) or by further *CFTR* physiologic testing.<sup>64-67</sup> Other articles in this Supplement present a discussion of the demonstration of *CFTR* dysfunction including the use of nasal potential difference (NPD) or intestinal current measurement (ICM) on the screen-positive newborn<sup>28</sup> and information on the symptomatic patient.<sup>9</sup>

## Next Steps for Intermediate Sweat Test Results

- (11) **All populations:** *The latest classifications identified in the Clinical and Functional Translation of CFTR (CFTR2) project<sup>20</sup> should be used to aid with CF diagnosis: (1) CF-causing mutation: individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed). (A sweat chloride test result  $\geq 30$  mmol/L is confirmatory for patients with this genotype); (2) mutation of varying clinical consequence: A mutation that in combination with a CF-causing mutation or another mutation of varying clinical consequence mutation may result in CF; (3) uncharacterized mutation/mutation of unknown clinical consequence: mutation that has not been evaluated by CFTR2 and may be disease causing or of variable clinical consequence or benign; and (4) non-CF-causing mutation: individuals with 1 or more are unlikely to have CF (as a result of that allele).*

The CFTR2 project provides a detailed characterization of CFTR mutations by collecting clinical and laboratory evidence of phenotypic consequence.<sup>20</sup> For each mutation, the CFTR2 website provides information and classification as listed above. The CFTR2 project is updated as mutation-specific functional analyses are completed. Also, because mutation categorization may change over time, it is important to confirm genotype interpretation on the most current version of the website. Mutations that are not analyzed as part of CFTR2 may still be interpretable if adequate research exists. For example, if a mutation is detected that is not annotated in CFTR2 and has been shown to be seen previously in patients with CF, has functional evidence that the nucleotide/protein change is deleterious; and does not occur commonly in databases of general (healthy) population, that mutation can be characterized as CF-causing.<sup>22</sup>

- (12) **All populations:** *In individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, the identification of 2 CF-causing mutations (defined by CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to confirm the diagnosis. A sweat chloride test result  $\geq 30$  mmol/L is confirmatory in individuals with 2 CF-causing mutations on separate chromosomes. As stated above, there are situations in which repeated sweat chloride testing does not provide further clarity, such as in individuals with CFTR mutations known to be associated with normal or intermediate sweat chloride.<sup>59,60</sup> Another article in this Supplement provides further exploration of this topic.<sup>9</sup>*
- (13) **All populations:** *The absence of detection of 2 CF-causing CFTR mutations does not exclude a diagnosis of CF. Because classification and identification of CF-causing CFTR mutations is ongoing, there are individuals with a CF diagnosis in whom 2 CFTR mutations have not been detected. Thus, even though the CFTR2 initiative has been a valuable step forward in improving the diagnostic characterization of patients with CFTR mutations, it does not*

take the place of clinical observation and expertise. Other articles in this Supplement present more in-depth discussions on this topic.<sup>9,22,29</sup>

To explore further a CF diagnosis in individuals with a positive newborn screen, symptoms of CF, or a positive family history, intermediate sweat chloride values (30–59 mmol/L), and fewer than 2 CF-causing mutations, the committee recommends additional CFTR physiological testing that directly measures CFTR function, such as NPD and ICM.<sup>68</sup>

- (14) **All populations:** *If further CF functional testing is needed (NPD and ICM), it should be performed in a validated reference center with trained staff certified by the CF Foundation Therapeutics Development Network or ECFS Clinical Trial Network. When performed correctly, NPD can discriminate a wide range of CFTR function.<sup>69,70</sup> ICM also can be used to confirm a diagnosis of CF in the context of intermediate sweat chloride levels,<sup>66-68,70-73</sup> and may be useful when NPD testing is unsuccessful (eg, when attempting to conduct NPD testing in the uncooperative child) (I Sermet-Gaudelus, personal communication, October 2015). Few CF centers in the US are prepared to conduct these tests. However, the added value that the results have provided to situations of diagnostic uncertainty (especially in Europe where they are more widely used) suggests that there will be widespread uptake of the tests in the future. There are patients with intermediate sweat chloride test results and an undefined CFTR genotype for whom NPD or ICM testing could provide diagnostic clarity; these patients should be seen in centers certified for the test in their country. Another article in this Supplement presents further discussion of NPD and ICM testing.<sup>28</sup>*
- (15) **For newborns:** *In individuals with a positive newborn screen but variable or uncharacterized CFTR mutations ( $< 2$  CF-causing mutations), the diagnosis of CF can be made by demonstrating CFTR dysfunction (a sweat chloride  $\geq 60$  mmol/L or CF-typical NPD or ICM). Identification of diagnostic levels for NPD and ICM measurements must be performed at the level of the reference center conducting the tests. Another article in this Supplement presents further discussion on this topic.<sup>28</sup>*

## For the Newborn with an Inconclusive Diagnosis

- (16) **For newborns:** *The term CRMS is used in the US for healthcare delivery purposes and CFSPID is used in other countries, but these both describe an inconclusive diagnosis following NBS. Newborn infants with a high level of immunoreactive trypsinogen (IRT) and inconclusive CFTR functional and genetic testing may be labeled either CRMS or CFSPID.<sup>25,26,29</sup> CFSPID describes the inconclusive nature of the condition in a manner that is easy for patients and families to understand and can be designated by International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code P09. However, because of the US healthcare*

system requirements,<sup>74</sup> CRMS (ICD-10 code E88.89) must be used in clinical settings in the US for continuing, follow-up care. These 2 terms are nearly identical, and the consensus committee recommends that the 2 terms be harmonized, for improved international communications and analysis of clinical outcomes. The term CRMS/CFSPID will be used throughout this Supplement and is recommended.<sup>75</sup>

- (17) **For newborns:** *The term CRMS/CFSPID is reserved for individuals who screen positive without clinical features consistent with a diagnosis of CF. The CRMS/CFSPID diagnosis should not be used in other clinical scenarios, including those involving individuals who have not received a positive NBS result, or individuals who have clinical symptoms attributable to CFTR dysfunction.*<sup>9</sup>
- (18) **For newborns:** *The definition of CRMS/CFSPID is an infant with a positive NBS test for CF and either: (1) sweat chloride value <30 mmol/L and 2 CFTR mutations, at least 1 of which has unclear phenotypic consequences; or (2) intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations. Individuals designated as CRMS/CFSPID initially appear asymptomatic and may never develop CF symptoms; however, they should be referred to a CF specialist at an accredited CF care center to ensure there are no hidden signs or symptoms of CF and to establish a plan for follow-up.*<sup>25,76</sup>

### Next Steps in the Newborn with CRMS/CFSPID Designation

- (19) **For newborns:** *Children designated as CRMS/CFSPID should undergo at least 1 repeat sweat chloride test at CF centers with suitable expertise, such as an accredited CF center. This test should be used to confirm the CRMS/CFSPID designation. Appropriate timing for the repeat sweat chloride test is discussed elsewhere in this Supplement.*<sup>29</sup>
- (20) **For newborns:** *Children designated as CRMS/CFSPID should have clinical evaluation performed by CF providers to identify the minority that may develop clinical symptoms. This group of children must be monitored for development of symptoms, and surveillance evaluations conducted (respiratory tract cultures, imaging, and spirometry or lung-clearance index when age-appropriate). Measuring fecal elastase levels or following IRT or pancreatitis associated protein trends may be considered if clinically indicated to identify CF clinical manifestations (phenotypes) objectively.<sup>11,25,76-78</sup> CF cannot be diagnosed through the identification of elevated levels of IRT alone; elevated IRT can occur in the context of other tissue stress.<sup>79,80</sup> Another article in this Supplement presents information about appropriate timing for monitoring.*<sup>29</sup>
- (21) **For newborns:** *Children designated as CRMS/CFSPID can be considered for extended CFTR gene analysis (sequencing and or deletion duplication testing), as well as CFTR functional analysis (NPD/ICM) testing to further define*

*their likelihood of developing CF. Other articles in this Supplement present information on the genetic tests that are useful in this scenario and useful functional analysis testing.*<sup>22,29</sup>

- (22) **For newborns:** *The decision to reclassify children designated as CRMS/CFSPID as CF is an integrated decision that should take into account functional assessment of CFTR (sweat chloride, and possibly NPD/ICM), CFTR genetic analysis, and clinical assessment by the CF clinicians caring for the patient. The decision to change a designation from CRMS/CFSPID to CF is a difficult one and should be made by an experienced CF physician.*<sup>25,26,29</sup>
- (23) **For newborns:** *Genetic counseling should be offered to families of individuals followed for CRMS/CFSPID, including a discussion of the risk in future pregnancies. The CF Foundation recommends that genetic counseling be offered to all families of newborns diagnosed with CF.<sup>24</sup> This is also important for families of newborns designated CRMS/CFSPID. Our understanding of the impact of various CFTR mutations is evolving and will continue to be clarified for many years. Genetic counseling is important for parents to understand the risk of a child having CF or being designated as CRMS/CFSPID in future pregnancies.*<sup>25,26</sup>
- (24) **For newborns (research recommendations):** *Infants with a designation of CRMS/CFSPID (by definition) do not have clinical features consistent with a diagnosis of CF and further research is needed to determine the prognosis and best practices for frequency and duration of follow-up. There is inadequate evidence to recommend a standard period and frequency for follow-up of these individuals. Further research on this will require common definitions, and the merging of CRMS and CFSPID designations is, therefore, especially timely.*

### General Note for the Nonscreened Individual

- (25) *For individuals presenting with CF symptoms, the same diagnostic criteria recommended for the screened population for sweat chloride testing, CFTR genetic analysis, and CFTR functional testing should be used to confirm a CF diagnosis. Although NBS encompasses the majority of new diagnoses, diagnosis of CF in the nonscreened population, particularly those born before the initiation of NBS at all accredited CF centers, still occurs. (There will also be individuals that present with symptoms following a false negative CF NBS result<sup>28,50</sup> who should then be considered as in the nonscreened population.) In these individuals, the diagnostic algorithm (Figure) remains applicable. However, the assignment of a diagnosis of CF will be weighed against alternative diagnostic explanations of the presenting symptom or feature. Therefore, the pretest probability of CF will influence the interpretation of sweat chloride testing, CFTR genetic analysis, or CFTR physiologic testing. Definitive diagnostic criteria for nonscreened populations include the presence of CF symptoms or a family history and sweat*



chloride  $\geq 60$  mmol/L OR presence of 2 CF-causing *CFTR* mutations and sweat chloride  $\geq 30$  mmol/L or physiologic testing demonstrating *CFTR* dysfunction.

The diagnosis of CF also can be appropriate if the above testing is not definitive, but *CFTR* dysfunction is the best explanation of the patient's symptoms. In keeping with the reasons for recommending genetic analysis of newborns diagnosed with CF (statement 7) or CRMS/CFSPID (statement 23), we suggest that all nonscreened individuals diagnosed with CF or a *CFTR*-related disorder also undergo genetic analysis, and they or their families be provided with genetic counseling to clarify the risk of disease in future pregnancies. Of course, as with all other diseases, it should be said that phenotype can vary in individuals with the same genotype.

### For the Nonscreened Individual with an Inconclusive Diagnosis

There are scenarios in which a given patient may not meet the above diagnostic criteria to be diagnosed with CF but also cannot be "ruled-out" as not having CF. Although this situation is similar to infants with CRMS/CFSPID, those classifications are not appropriate for the nonscreened populations.

- (26) *The diagnosis of CFTR-related disorder has been defined as a monosymptomatic clinical entity (congenital bilateral absence of the vas deferens/pancreatitis/bronchiectasis) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF. Individuals with a CFTR-related disorder<sup>27</sup> (generally mono-organ) should be assessed and followed by a CF physician to ensure that if any additional symptoms develop that are typical of CF, they are detected.<sup>9</sup>*
- (27) *Clinicians should avoid the use of terms such as classic/nonclassic CF, typical/atypical CF, and delayed CF, because*

*these terms have no harmonized definition and could be confusing for families or caregivers. In these and other situations, education on clinical entities and organ pathologies associated with CF and their relationship with *CFTR*-related disorder should be provided to patients, families, and primary care providers to aid in the early recognition of symptoms of CF. The CF Foundation reaffirms the view that it is essential to avoid confusion of parents and patients, and also caregivers, with imprecise terms like atypical or nonclassic because early diagnosis and more effective treatments can lead to relatively mild disease for many years even in c.1521\_1523delCTT (legacy: F508del) homozygotes. However, it is understood that some European countries will continue to use such terminology as they pursue research on mild cases.*

### ICD-10 Codes for Individuals with *CFTR* Dysfunction

The ICD<sup>81</sup> system is a medical classification list created collaboratively by the World Health Organization to be "the international standard for defining and reporting diseases and health conditions. It allows the world to compare and share health information using a common language."<sup>82</sup> It is an alphanumeric system containing codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. The ICD system is valuable, indeed essential, for many purposes including: (1) entry and continuation into the healthcare delivery mechanisms of some countries such as the US where the ICD codes are an integral and required component of billing; (2) coding death certificates internationally, thus, allowing assessment of mortality data; (3) epidemiologic research; and (4) medical economics research.

**Table II. ICD-10 codes for use in individuals with CF and other *CFTR* dysfunctional diseases or disorders**

Diseases/disorders	Primary ICD-10 code	Secondary ICD-10 code
CF, unspecified	E84.9	
CF, with meconium ileus	E84.11	
CF, with other intestinal manifestations (eg, DIOS)	E84.19	
CF, with pulmonary manifestations	E84.0	Use secondary code for details such as infectious organisms present (eg, B96.5 for <i>Pseudomonas aeruginosa</i> )
CF, with acute pneumothorax	E84.09	J93.83
CF, with pneumothorax not otherwise specified	E84.09	J93.9
CF, with hemoptysis	E84.09	R04.2
CRMS, metabolic disorder unspecified	E88.89	
CFSPID	P09 (abnormal findings on neonatal screening)* Or: E88.89 (if CRMS/CFSPID is adopted as the preferred terminology)	
CFTR-related disorder (Code the signs/symptoms as described but do not use E84.9)		
Pancreatitis, recurrent	K85.9	} Z14.1 (CF carrier status)
CBAVD	Q55.4 <sup>†</sup>	
Bronchiectasis, chronic acquired	J47.9	

DIOS, distal intestinal obstruction syndrome.

\*Describes positive newborn screen result with an inclusive diagnosis but only applies to the newborn period and thus cannot be used in follow-up care.

<sup>†</sup>Preferred over N46.025 (azoospermia because of a systemic disease).



The most recent revision of the system, ICD-10, implemented in October 2015, provides more than 14 400 different codes and can be expanded to over 16 000 codes by using optional subclassifications. It is not possible to convert ICD *Ninth Revision* datasets to ICD-10. In the ICD-10 coding system, characters 1-3 indicate the category of disease; 4-6 indicate etiology, anatomic site, severity or other clinical detail of disease; and character 7 is a placeholder for extending the code to increase specificity. The designation “E” indicates endocrine, nutritional, and metabolic diseases, and “J” applies to diseases of the respiratory system.

Some CF specialists were engaged in the ICD-10 development process, but the degree of influence was limited, and coding for diseases or disorders caused by CFTR dysfunction is not ideal, including the absence of a code for CFTR-related disorder. The current ICD-10 code is undergoing revision to ICD *11th Revision* which is due to be completed in 2018. Participation is invited (<http://www.who.int/classifications/icd/revision/en/>), and we encourage involvement by CF caregivers.

A list of ICD-10 codes that should be used in the delivery of care for those disorders associated with *CFTR* mutations

(that is, CF, CRMS/CFSPID, and CFTR-related disorder) is shown in **Table II**.

### Summary of Revisions to the 2008 CF Foundation Guidelines

The basic strategy necessary for diagnosis of CF in the large majority of individuals remains unchanged from the process recommended in 2008.<sup>24</sup> However, some of the diagnostic tools presented in this document and the recommended application of those tools in more complex clinical scenarios do represent significant changes. A summary of the main changes to the 2008 diagnostic algorithm is presented in **Table III**.

### Discussion

Although NBS is now widely implemented, the diagnosis of CF is not always clear. A sweat test is required for confirmation of CF; a sweat chloride level  $\geq 60$  mmol/L indicates a diagnosis of CF and a sweat chloride level  $< 30$  mmol/L indicates

**Table III. Summary of revisions to the 2008 CF Foundation guidelines for diagnosis of CF**

Revisions to guidelines for screened populations	
2015 Consensus	2008 <sup>24</sup> Comparison
<ul style="list-style-type: none"> <li>Sweat testing: same recommendation in 2008, but is not being followed and is, therefore, re-emphasized here</li> <li>Sweat Cl<sup>-</sup>: <math>&lt; 30</math> mmol/L is normal threshold for all ages (exceptions occur)</li> <li>NPD/ICM: useful; testing should be conducted in a validated lab</li> <li>CFTR mutations: use CFTR2 mutation list, with guidelines given for mutations not included in CFTR2</li> <li>Presumptive diagnosis of CF: can be made (NBS<sup>+</sup> and 2 CF mutations or signs and symptoms of CF; or meconium ileus) and treatment started; diagnosis must be confirmed with a sweat test</li> <li>Genetic analysis: recommended in addition to that done during NBS</li> </ul>	<ul style="list-style-type: none"> <li>Sweat testing: should be done in everyone</li> <li>Sweat Cl<sup>-</sup>: <math>&lt; 40</math> mmol/L was normal threshold for ages <math>\geq 6</math> mo (exceptions occur)</li> <li>NPD: limited to contributory evidence; ICM: used only in research</li> <li>CFTR mutations: Used ACMG/ACOG panel of 23 mutations<sup>51</sup></li> <li>Not discussed</li> <li>Genetic analysis: recommended if not part of NBS</li> </ul>
Revisions to guidelines for CRMS/CFSPID	
2015 Consensus	2008 <sup>24</sup> Comparison
<ul style="list-style-type: none"> <li>CRMS = CFSPID: now a harmonized definition</li> <li>Repeat sweat testing recommended; NPD/ICM testing may be considered</li> <li>Clinical assessment: by age 2 mo; duration and frequency of follow-up remains to be determined</li> </ul>	<ul style="list-style-type: none"> <li>(Neither term in use)</li> <li>Repeat sweat testing: every 6-12 mo, but recommendation considered to be “evolving”</li> <li>Clinical assessment: by age 2 mo; repeat every 6-12 mo</li> </ul>
Revisions to guidelines for nonscreened population with inconclusive sweat chloride values	
2015 Consensus	2008 <sup>24</sup> Comparison
<ul style="list-style-type: none"> <li>Sweat Cl<sup>-</sup>: <math>&lt; 30</math> mmol/L is normal threshold for all ages (exceptions occur)</li> <li>Ancillary testing: NPD/ICM</li> </ul>	<ul style="list-style-type: none"> <li>Sweat Cl<sup>-</sup>: <math>&lt; 40</math> mmol/L was normal threshold for ages <math>\geq 6</math> mo (exceptions occur)</li> <li>Ancillary testing: NPD only</li> </ul>
Revisions to general definitions	
2015 Consensus	2008 <sup>24</sup> Comparison
<ul style="list-style-type: none"> <li>CFTR-related disorder: a symptomatic entity that does not meet diagnostic criteria for CF</li> <li>Avoid terms like “atypical” or “nonclassical” CF because there is no consensus definition of these terms</li> </ul>	<ul style="list-style-type: none"> <li>CFTR-related disorder: Individuals with 0-1 CF-causing mutations and clinical signs (possibly multiple-organ) suggestive of CF</li> <li>Recommendation unchanged but greater emphasis now given to the importance of avoiding these imprecise, potentially confusing terms in the US.</li> </ul>

ACMG/ACOG, American College of Medical Genetics/American Congress of Obstetricians and Gynecologists.

that CF is unlikely. In individuals who fall into the intermediate sweat chloride level, 30-59 mmol/L, genetic analysis is required. Further testing for CFTR function such as NPD and ICM may also be indicated but should be performed in a specialized center approved for such studies. Some infants with a positive NBS and sweat chloride levels from 30 to 59 mmol/L or even  $\leq 29$  mmol/L and inconclusive genetic testing may be designated as CRMS/CFSPID. Further research is needed to determine their prognosis, best practice, and frequency of follow-up. ■

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## Appendix

Additional members of the Cystic Fibrosis Foundation Committees and 2015 Cystic Fibrosis Foundation Diagnosis Consensus Conference Executive Subcommittee include:

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