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3 **INSTRUCTIONS:**

4
5 **SECTION 1:** Enter your role and association with the CF community.

6
7 **SECTION 2:** Review the recommendation statements found in the Table, on
8 pages 18-22 in **Diagnosis_of_CF_Consensus_Guidelines.pdf**. This section
9 includes questions that will ask you to select a recommendation number and
10 provide you with space for comments.

11
12 **SECTION 3:** To capture comments and feedback on the body of the
13 manuscript, please select a page number and type in the line number
14 corresponding to your comment and/or suggested change.

15
16 **SECTION 4:** To capture comments on the other table and figure you will be
17 prompted to refer to the figure on pages 23-24.

DRAFT

19 **Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation**

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40 **Notation of no reprints**

41

42

43 **List of key words not in the title:** newborn screening, CFTR-related metabolic syndrome, CF-

44 screen positive, inconclusive diagnosis, immunoreactive trypsinogen, pancreatitis associated

45 protein, sweat test, nasal potential difference, intestinal current measurement

46

47 **Source of funding and conflict of interest statement, if applicable:**

48

49 Funded by the Cystic Fibrosis Foundation. Conflicts of interest:

50 **ABSTRACT**

51
52 **Background:** Cystic fibrosis (CF), caused by mutations in the gene for the cystic fibrosis
53 transmembrane conductance regulator gene (*CFTR*), continues to present diagnostic challenges.
54 Newborn screening and an evolving understanding of CF genetics have prompted a
55 reconsideration of the diagnosis consensus criteria.

56
57 **Methods:** To improve diagnosis and achieve standardized definitions worldwide, the CF
58 Foundation convened a committee of 32 experts in CF diagnosis from 9 countries to develop
59 clear and actionable consensus guidelines on the diagnosis of CF and to clarify diagnostic criteria
60 and terminology for other disorders associated with *CFTR* mutations. An *a priori* threshold of
61 ≥80% affirmative votes was required for acceptance of each statement.

62
63 **Results:** After reviewing relevant literature, the committee convened to review evidence and
64 cases. Following the conference, consensus statements were developed by an executive
65 subcommittee. The entire consensus committee voted and approved 27 of 28 statements, 7 of
66 which needed revisions and another round of voting.

67
68 **Conclusions:** It is recommended that diagnoses associated with *CFTR* mutations in all
69 individuals from newborn to adult be established by evaluation of *CFTR* function with a sweat
70 chloride test. The latest mutation classifications annotated in the CFTR2 project
71 (<http://www.cftr2.org/index.php>) should be used to aid in diagnosis. Newborns with a high
72 immunoreactive trypsinogen level and inconclusive *CFTR* functional and genetic testing may be
73 designated *CFTR*-related metabolic syndrome (CRMS) or CF Screen Positive, Inconclusive
74 Diagnosis (CFSPID); these terms are now merged and equivalent, and CRMS/CFSPID may be
75 used. ICD-10 codes for use in diagnoses associated with *CFTR* mutations are included.

76
77 250/250 words

78 **INTRODUCTION**

79

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

86

87 A diagnosis of CF initially relied on phenotype, with clinical recognition of characteristic signs
88 and symptoms.⁸ (See also Addendum for J Pediatrics Manuscript (MS) #6, which is being
89 drafted.) However, due to widespread CF newborn screening (NBS), at least 64% of new CF
90 diagnoses in the United States now occur in asymptomatic or minimally symptomatic infants
91 following a positive NBS result.⁹ Although the majority of these screen-positive infants can be
92 readily diagnosed with CF after a confirmatory test showing high sweat chloride concentration,
93 the diagnosis is not clear in some individuals,^{10,11} leading to persistent challenges¹² and stresses,
94 and importantly including a potentially disturbed parent/child relationship.^{13–15} Furthermore,
95 universal NBS was implemented only recently in the United States, and many individuals born
96 there prior to 2010 have not been screened. Diagnosis of CF in the nonscreened population can
97 be challenging, because the age of onset and severity of symptoms as a result of *CFTR*
98 dysfunction can be highly variable. Symptoms can include subtle presentations of pancreatitis or
99 respiratory symptoms in older children and adults, nasal polyposis, and male infertility).^{16–18}
100 (See also Addendum for J Pediatrics MS #6, which is being drafted.)

101

102 The last few years have seen significant growth of phenotypic and genotypic information on CF
103 that can help with interpretation of the disease status in many of these patients. International
104 collection of clinical data from individuals with CF¹⁹ and laboratory advances²⁰ provide
105 functional insight into the physiological impact of the most common mutations (see Addendum
106 for J Pediatrics MS #3, which is being drafted). Due to this new information, and to seek
107 harmony with the diagnostic criteria and terminology²¹ of the European Cystic Fibrosis Society

108 (ECFS), it was decided that the 2008 diagnostic guidelines²² of the Cystic Fibrosis Foundation
109 (CF Foundation) should be revised.

110

111 The CF Foundation convened a committee of 32 experts in the diagnosis of CF from nine
112 countries to update diagnostic guidance and achieve standardization in definitions worldwide.

113 The mission of this committee was to develop clear and actionable consensus guidelines on
114 diagnosis of CF and other conditions associated with mutations in the *CFTR* gene such as CFTR-
115 related metabolic syndrome (CRMS)²³ or CF Screen Positive, Inconclusive Diagnosis
116 (CFSPID),²⁴ and CFTR-related disorder.²⁵ The recommendations in this document address
117 individuals with both clear and unclear diagnosis, including infants with positive NBS and/or
118 prenatal diagnosis (see Addendum for J Pediatrics MS #4, which is being drafted), and
119 individuals with CF-like symptoms who were either never screened or who had false negative
120 newborn or prenatal screening results (see Addendum for J Pediatrics MS #6, which is being
121 drafted). Case studies, designed to show how the recommendations should be applied in
122 challenging clinical scenarios, can be found in additional manuscripts created as a result of this
123 conference, published as Supplement X of *The Journal of Pediatrics* (see Addendum for J
124 Pediatrics MS #3-#6).

125

126

127 **METHODS**

128

129 An international consensus committee of 32 experts was purposively selected and tasked with
130 the development of guidelines on the diagnosis of CF. Committee selection was determined to
131 include participants representative of worldwide CF care communities, particularly pediatric
132 CF providers with NBS experience, and other relevant specialists including adult CF providers.
133 The committee first reviewed the existing CF Foundation diagnosis guidelines,²² a list of

134 publications on CF diagnosis published since the 2008 CF Foundation Diagnosis Guidelines,
135 and 10 articles selected by conference co-chairs. An executive subcommittee consisting of 10
136 representatives from 4 countries was established prior to the October 2015 North American CF
137 Conference (NACFC).

138

139 The consensus conference was held prior to the 2015 NACFC. At this conference, the
140 committee presented and discussed new studies and data on CF diagnosis. An executive
141 subcommittee developed the consensus statements at subsequent meetings. These statements
142 were reviewed by the consensus committee and voted on by the members using an electronic
143 survey tool (SurveyMonkey).²⁶ Individuals voting against a statement were asked to provide a
144 revised statement or explanation. An *a priori* threshold of $\geq 80\%$ affirmative votes was
145 required for acceptance. Statements that did not reach 80% agreement with the associated
146 committee feedback were reviewed by the committee co-chairs and revised with input from the
147 rest of the executive subcommittee.

148

149 After the recommendation statements were agreed upon, they were presented to the European
150 CF Society (ECFS) at the Diagnostic Network Working Group annual meeting in February
151 2016 to help engage all parties in the discussion. The manuscript was distributed for feedback
152 from the executive subcommittee, conference committee, the CF Foundation's CF Center
153 Committee, all the CF centers in the United States, parents of screened infants, and to a variety
154 of international organizations and their members for a public comment period.

155

156 **RESULTS AND DISCUSSION**

157

158 In the survey, participants were able to vote in agreement, disagreement, or to abstain. One
159 committee member did not participate in this vote. Of the 28 statements initially voted on, 8
160 did not reach at least 80% agreement. The 8 statements that did not pass were reviewed and
161 revised, and reduced to seven statements by the chairs and the executive committee and sent
162 out for a second round of voting. All but one of the 32 committee members participated in this
163 vote. All 7 of the revised statements passed in the second round of voting. For additional
164 detail and a historical perspective please see other articles in the supplement.

165
166 The committee approved 27 consensus statements (**Table I**) in 4 overlapping categories that
167 apply to:
168 1. Both screened and nonscreened populations;
169 2. Screened pediatric populations, ie, fetuses undergoing prenatal testing and neonates;
170 3. Infants with uncertain diagnosis and designated either CRMS or CFSPID (now
171 considered to be the same)
172 4. Patients presenting clinically who represent nonscreened populations, including children
173 born at home or in regions before NBS implementation, those with false negative
174 screening tests, and older individuals.
175
176 The **Figure** provides a simplified algorithm for how these consensus statements should be
177 applied to individuals under suspicion of CF. Even though many individuals enter this algorithm
178 through a positive newborn screen in which *CFTR* genetic testing was done, the diagnosis of CF
179 is primarily based on the demonstration of abnormal *CFTR* function by measurement of chloride
180 concentration in the sweat.²² Although obtaining an adequate sweat specimen for chloride
181 measurements can be challenging, particularly in very young infants, experience and studies
182 have shown that this is feasible in full-term infants during the first postnatal month, ie, during the
183 neonatal period.^{27–30} Following the committee's recommendations, shown below, will improve
184 reliability of the result.
185
186 **1. All Populations:** Sweat chloride testing should be performed according to approved
187 procedural guidelines published in established, international protocols such as the CLSI
188 **2009 Guidelines.**
189 Following appropriate protocols for performing the sweat test²⁸ is important for achieving
190 accurate results and minimizing collection of inadequate amounts of sweat (quantity not
191 sufficient, QNS).^{29–33} (See also Addendum for J Pediatrics MS #4, which is being drafted.)
192
193 **2. For Newborns:** Newborns with a positive CF newborn screen, to increase the
194 likelihood of collecting an adequate sweat specimen, should have the test performed

195 **bilaterally and when the infant weighs > 2 kg, and is at least 36 weeks of corrected**
196 **gestational age.**

197 Sweat samples collected bilaterally must not be combined; rather, they should be
198 analyzed separately, providing a useful quality control measure.²⁹

200 **3. For Newborns: Newborns greater than 36 weeks gestation and 2 kg body weight**
201 **with a positive CF newborn screen, or positive prenatal genetic test, should have**
202 **sweat chloride testing performed as soon as possible after 10 days of age, ideally by**
203 **the end of the neonatal period (4 weeks of age).**

204 Timing of the sweat chloride test is crucial in newborns.³⁴ Sweat testing can occur as
205 early as 48 hours after birth,²⁵ but most NBS results will not be available by that time.
206 However, testing should occur before the end of the neonatal period because malnutrition
207 and other risks such as dehydration may be present even in the first few weeks of life.³⁵⁻³⁸

209 **4. For Newborns: In infants with presumptive CF identified through NBS, CF**
210 **treatment should not be delayed while efforts to establish a diagnosis of CF are**
211 **initiated.**

212 Optimal outcomes depend on early intervention. Efforts to obtain adequate quantities of
213 sweat and accurate sweat chloride values should not delay start of salt supplementation or
214 other appropriate therapies.³⁹ The CF Foundation recommends that infants with CF have
215 an initial visit at an accredited CF care center within 24-72 hours of diagnosis,³⁹ and
216 timing of the initial visit for infants with a presumptive diagnosis should aim to meet this
217 timeframe. A presumptive diagnosis of CF for purposes of treatment initiation can
218 include the following clinical circumstances:

- 219 • A positive CF newborn screen showing 2 CF-causing *CFTR* mutations (see
220 below)
- 221 • A positive CF newborn screen AND clinical signs and symptoms of CF
- 222 • Meconium ileus, with or without a positive newborn screen.

223 However, definitive diagnosis requires demonstration of *CFTR* dysfunction.

225 **5. All Populations:** Sweat chloride analysis should be performed within a few hours of
226 sweat collection and the results and interpretations should be reported to clinicians and
227 parents or patients, as soon as possible and certainly on the same day.

228 Prompt reporting should be made regardless of sweat test results.⁴⁰⁻⁴³ A second, confirmatory,
229 sweat test is not necessary, nor is it likely to be reimbursable; this is a change from previous CF
230 Foundation diagnostic guidelines.^{22,44}

231

232 **SWEAT CHLORIDE TEST RESULTS \geq 60 MMOL/L**

233 **6. All Populations:** In individuals presenting with a positive newborn screen, clinical
234 features consistent with CF, or a positive family history, a diagnosis of CF can be made if
235 the sweat chloride value is \geq 60 mmol/L.

236 While the sweat test is commonly used for diagnosis of individuals presenting with symptoms of
237 CF, many newborns are reported as having CF based solely on a positive NBS result. However,
238 NBS tests must always be considered screening procedures and not diagnostic studies. The
239 genetic analysis included as part of many NBS programs must not be relied upon for conclusive
240 diagnosis, as errors can arise from problems with the Guthrie card,⁴⁵ changes in the mutation
241 panel utilized by the NBS program (for example, see ref. 46), or detection of 2 *CFTR* mutations
242 in *cis* (ie, on the same chromosome).⁴⁷ (See also Addendum for J Pediatrics MS #3, which is
243 being drafted.)

244

245 **7. For Newborns:** Individuals who are screen-positive and meet sweat chloride
246 criteria for CF diagnosis should undergo *CFTR* genetic testing if the *CFTR* genotype
247 was not available through the screening process or is incomplete.

248 Genetic testing is an important part of the diagnostic work-up, and it is not uncommon for
249 a positive NBS result to include the recognition of 2 CF-causing mutations. The
250 screening result should be confirmed in a clinical genetics laboratory, even if a sweat
251 chloride result is positive. The genetic testing results now have additional value in
252 therapy selection.⁴⁸

253

254 **SWEAT CHLORIDE TEST RESULTS $<$ 29 MMOL/L**

255 **8. For Newborns:** In individuals with a positive newborn screen, a sweat chloride of
256 less than 30 mmol/L indicates that CF is unlikely.

257

258 **9. All Populations:** Individuals with clinical features that may be consistent with CF who
259 have a sweat chloride less than 30 mmol/L indicates that CF is less likely. It may however
260 be considered if evolving clinical criteria and/or *CFTR* genotyping support CF and not an
261 alternative diagnosis.

262 Note that the upper limit for a normal sweat chloride is 29 mmol/L for all age groups. This is a
263 change from previous guidelines for people > 6 months of age (the previous upper limit of
264 normal was 39 mmol/L).

265

266 See Addendum for J Pediatrics MS #3 (which is being drafted) for more details regarding the
267 diagnosis of CF in the very rare individual with sweat chloride \leq 29 mmol/L.¹⁹ Some *CFTR*
268 mutations, such as c.3717+12191C>T (legacy name 3849+10kb C->T), are associated with low
269 sweat chloride values; in these cases an alternative diagnosis does not need to be ruled out.^{49,50}
270 (See also Addendum for J Pediatrics MS #6, which is being drafted.)

271

SWEAT CHLORIDE TEST RESULTS OF 30-59 MMOL/L

272 **10. All Populations:** Individuals presenting with a positive newborn screen, symptoms of
273 CF, or a positive family history, and sweat chloride values in the intermediate range (30-59
274 mmol/L) on two separate occasions may have CF. They should be considered for extended
275 *CFTR* gene analysis and/or *CFTR* functional analysis.

276 Individuals with sweat chloride concentrations in the intermediate range will need further study
277 to establish or rule out a CF diagnosis.^{11,51,52} Evidence may be provided by *CFTR* genotype.¹⁹
278 (See Addendum for J Pediatrics MS #3, which is being drafted to discuss *CFTR* genetic testing
279 and interpretation in detail) or by further *CFTR* physiologic testing.⁵³⁻⁵⁶ For discussion of
280 demonstration of *CFTR* dysfunction including the use of nasal potential difference (NPD) or
281 intestinal current measurement (ICM) on the screen-positive newborn see Addendum for J
282 Pediatrics MS #4, which is being drafted; see MS #6 for information on the symptomatic
283 patient).

286 **NEXT STEPS FOR INTERMEDIATE SWEAT TEST RESULTS**

287 **11. All Populations:** The latest classifications identified in the CFTR2 project

288 [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis:

- 289 • **CF-causing mutation:** Individuals with 2 copies on separate alleles will likely have
290 CF (clinical sweat confirmation needed)
- 291 • **Mutation of varying clinical consequence (MVCC):** a mutation that in combination
292 with a CF-causing mutation or another MVCC mutation may result in CF
- 293 • **Uncharacterized mutation/mutation of unknown clinical consequence (UNK):**
294 mutation that has not been evaluated by CFTR2 and may be disease-causing or of
295 variable clinical consequences or benign
- 296 • **Non-CF causing mutation:** individuals with 1 or more are unlikely to have CF (as a
297 result of that allele)

298 The Clinical and Functional Translation of CFTR (CFTR2) project provides a definitive
299 characterization of *CFTR* mutations by collecting clinical and laboratory evidence of phenotypic
300 consequence.¹⁹ For each mutation, the CFTR2 website provides information and classification
301 as listed above. The CFTR2 project is updated as mutation functional analyses are completed.
302 Because mutation categorization may change over time, it is important to confirm genotype
303 interpretation on the most current version of the website.

304

305 **12. All Populations:** In individuals presenting with a positive newborn screen, symptoms of
306 CF, or a positive family history, the identification of 2 CF-causing mutations (defined by
307 CFTR2) is consistent with a diagnosis of CF. Sweat chloride testing is necessary, though, to
308 confirm the diagnosis.

309 As stated above, there are situations in which repeated sweat chloride testing does not provide
310 further clarity, such as in individuals with *CFTR* mutations known to be associated with a normal
311 sweat chloride.^{49,50} (See Addendum for J Pediatrics MS #3, which is being drafted, for further
312 exploration of this topic).

313

314 **13. All Populations:** The absence of detection of 2 CF-causing *CFTR* mutations does not
315 exclude a diagnosis of CF.

316 Because classification and identification of CF-causing *CFTR* mutations is ongoing, there are
317 individuals with CF in whom 2 *CFTR* mutations have not been detected. Thus, while the CFTR2
318 initiative has been a valuable step forward in improving the diagnostic characterization of
319 patients with *CFTR* mutations, it does not take the place of clinical observation and expertise.
320 (See Addendum for J Pediatrics Manuscripts #3, #5, and #6, being drafted for more in-depth
321 discussion.)

322

323 To further explore a CF diagnosis in individuals with a positive newborn screen, symptoms of
324 CF, or a positive family history, intermediate sweat chloride values (30-59 mmol/L) and fewer
325 than 2 CF-causing mutations, the committee recommends additional *CFTR* physiological testing.
326 Clinical electrophysiological tests that directly measure *CFTR* function, such as NPD and ICM
327 may be useful to confirm a diagnosis of CF.⁵⁷

328

329 **14. All Populations: If further CF functional testing is needed (NPD and ICM), it should**
330 **be performed in a validated reference center with trained staff certified by the CF**
331 **Foundation Therapeutics Development Network (TDN) or ECFS Clinical Trial Network**
332 **(CTN).**

333 When performed correctly, NPD can discriminate between a wide range of *CFTR* function.⁵⁸⁻⁶⁰
334 ICM can be used to confirm a diagnosis of CF in the context of intermediate sweat chloride
335 levels,^{55,56,60-63} and may be useful when NPD testing is unsuccessful (for example, when
336 attempting to conduct NPD testing in the uncooperative child).⁶⁴ (See also Addendum for J
337 Pediatrics MS #4, which is being drafted.)

338

339 **15. For Newborns: In individuals with a positive newborn screen but variable or**
340 **uncharacterized *CFTR* mutations (<2 CF-causing mutations), the diagnosis of CF**
341 **can be made by demonstrating *CFTR* dysfunction (a sweat chloride \geq 60 mmol/L or**
342 **CF-typical NPD or ICM).**

343

344 **FOR THE NEWBORN WITH AN INCONCLUSIVE DIAGNOSIS**

345 **16. For Newborns:** The term CRMS is used in the United States for health care
346 delivery purposes and CFSPID is used in other countries, but these both describe an
347 inconclusive diagnosis following NBS.

348 Newborn infants with a high level of immunoreactive trypsinogen (IRT) and inconclusive
349 CFTR functional and genetic testing may be labelled either CRMS²³ or CFSPID.²⁴ (See
350 also Addendum for J Pediatrics MS #5, which is being drafted.) CFSPID describes the
351 inconclusive nature of the condition in a manner that is easy for patients and families to
352 understand and can be designated by ICD-10 code P09. However, due to US health care
353 system requirements (see Addendum for J Pediatrics MS #2, which is being drafted),
354 CRMS (ICD-10 code E88.89) must be used in clinical settings of the USA for continuing,
355 follow-up care. These two terms are nearly identical, and the Consensus Committee
356 recommends that the two terms be harmonized, for improved international
357 communications and analysis of clinical outcomes. The term CRMS/CFSPID will be
358 used throughout this supplement and is recommended.⁶⁵

360 **17. For Newborns:** The term CRMS/CFSPID is reserved for screen-positive
361 individuals without clinical features consistent with a diagnosis of CF.

362 The CRMS/CFSPID diagnosis should not be used in other clinical scenarios, including
363 those involving individuals who have not received a positive NBS result, or individuals
364 who have clinical symptoms attributable to CFTR dysfunction (see Addendum for J
365 Pediatrics MS #6, which is being drafted).

367 **18. For Newborns:** The definition of CRMS/CFSPID is an infant with a positive
368 NBS test for CF and either:

- 369 • A sweat chloride value less than 30 mmol/L and 2 CFTR mutations, at least 1
370 of which has unclear phenotypic consequences
371 OR
372 • An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing
373 mutations

374 Individuals designated as CRMS/CFSPID should be seen at an accredited CF care center
375 to ensure there are no hidden signs or symptoms of CF and to establish a plan for
376 follow-up.^{23,66}

377

378 NEXT STEPS IN THE NEWBORN WITH CRMS/CFSPID DESIGNATION

379 (For detailed information see Addendum for J Pediatrics MS #5.)

380 **19. For Newborns:** Children designated as CRMS/CFSPID should undergo at least
381 one repeat sweat chloride test at CF centers with suitable expertise, such as an
382 accredited CF center.

383 This test should be used to confirm the CRMS/CFSPID designation. Appropriate timing
384 for the repeat sweat chloride test is discussed in J Pediatrics MS #5 (being drafted; see
385 Addendum).

386

387 **20. For Newborns:** Children designated as CRMS/CFSPID should have clinical
388 evaluation performed by CF providers to identify the minority that may develop
389 clinical symptoms.

390

391 **21. For Newborns:** Children designated as CRMS/CFSPID can be considered for
392 extended *CFTR* gene analysis (sequencing and or deletion duplication testing), as
393 well as *CFTR* functional analysis (NPD/ICM) testing to further define their
394 likelihood of developing CF.

395

396 **22. For Newborns:** The decision to reclassify children designated as CRMS/CFSPID
397 as CF is an integrated decision that should take into account functional assessment
398 of *CFTR* (sweat chloride, and possibly NPD/ICM), *CFTR* genetic analysis, and
399 clinical assessment by the CF clinicians caring for the patient.

400 The decision to change a designation from CRMS/CFSPID to CF is a difficult one and
401 should be made by an experienced CF physician.^{23,24} (See also Addendum for J
402 Pediatrics MS #5, which is being drafted.) Monitoring symptoms, surveillance
403 evaluations (respiratory tract cultures, imaging, and spirometry or lung-clearance index
404 when age-appropriate), and measuring fecal elastase levels or following IRT or

405 pancreatitis associated protein (PAP) trends may be considered if clinically indicated and
406 to objectively identify CF clinical manifestations (phenotypes).^{10,23,54,56,66–68} CF cannot
407 be diagnosed through the identification of elevated levels of IRT, which can occur in the
408 context of other tissue stress.^{69,70}

409

410 **23. For Newborns:** Genetic counseling should be offered to families of individuals
411 followed for CRMS/CFSPID, including a discussion of the risk in future
412 pregnancies.

413 Our understanding of the impact of various *CFTR* mutations is evolving and will
414 continue to be clarified for many years. Genetic counseling is important for parents to
415 understand the risk of a child having CF or being designated as CRMS/CFSPID in future
416 pregnancies.^{23,24}

417

418 **24. For Newborns, Research Recommendation:** Infants with a designation of
419 CRMS/CFSPID (by definition) do not have clinical features consistent with a
420 diagnosis of CF and further research is needed to determine the prognosis and best
421 practices for frequency and duration of follow up.

422 There is inadequate evidence to recommend a standard period and frequency for follow-
423 up of these individuals. Further research on this will require common definitions, and the
424 merging of CRMS and CFSPID designations is therefore especially timely.

425

426 **GENERAL NOTE FOR THE NONSCREENED INDIVIDUAL**

427 **25. For individuals presenting with CF symptoms, the same diagnostic criteria
428 recommended for the screened population for sweat chloride testing, *CFTR* genetic
429 analysis, and *CFTR* functional testing should be used to confirm a CF diagnosis.**

430 Although NBS encompasses the majority of new diagnoses, diagnosis of CF in the nonscreened
431 population, particularly those born before the initiation of NBS at all accredited CF centers, still
432 occurs. In these individuals, the diagnostic algorithm (**Figure**) remains applicable. However,
433 the assignment of a diagnosis of CF will be weighed against alternative diagnostic explanations
434 of the presenting symptom or feature. Therefore, the pre-test probability will influence the
435 interpretation of sweat chloride testing, *CFTR* genetic analysis, or *CFTR* physiologic testing.

436 Definitive diagnostic criteria for nonscreened populations include the presence of CF symptoms
437 OR a family history and:

- 438 • Sweat chloride \geq 60 mmol/L
- 439 OR
- 440 • The presence of 2 CF-causing *CFTR* mutations
- 441 OR
- 442 • Physiologic testing demonstrating *CFTR* dysfunction.

443 The diagnosis of CF can also be appropriate if the above testing is not definitive, but *CFTR*
444 dysfunction is the best explanation of the patient's symptoms, and CF therapies would improve
445 the patient's condition.

446

447 FOR THE NONSCREENED INDIVIDUAL WITH THE INCONCLUSIVE DIAGNOSIS

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

452

453 **26. The diagnosis of *CFTR*-related disorder has been defined as a monosymptomatic
454 clinical entity [CBAVD/pancreatitis/bronchiectasis] associated with *CFTR* dysfunction that
455 does not fulfill the diagnostic criteria for CF.**

456 Individuals with a monosymptomatic *CFTR*-related disorder²⁵ should be assessed and followed
457 by a CF physician. (See Addendum for J Pediatrics MS #6, which is being drafted.)

458

459 **27. Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF,
460 delayed CF, since these terms have no harmonized definition and could be confusing for
461 families or caregivers.**

462 In these and other situations, education on clinical entities and organ pathologies associated with
463 CF and their relationship with *CFTR*-related disorder, should be provided to patients, families,
464 and primary care providers to aid in the early recognition of symptoms of CF.

465

466 ICD-10 CODES FOR INDIVIDUALS WITH *CFTR* DYSFUNCTION

467 The International Statistical Classification of Diseases and Related Health Problems (ICD)⁷¹
468 system is a medical classification list created collaboratively by the World Health Organization
469 (WHO) to be “the international standard for defining and reporting diseases and health
470 conditions. It allows the world to compare and share health information using a common
471 language.”⁷² It is an alphanumeric system containing codes for diseases, signs and symptoms,
472 abnormal findings, complaints, social circumstances, and external causes of injury or diseases.
473 The ICD system is valuable, indeed essential, for many purposes including: 1) entry and
474 continuation into the healthcare delivery mechanisms of some countries such as the United States
475 where the ICD codes are an integral and required component of billing; 2) coding death
476 certificates internationally, thus allowing assessment of mortality data; 3) epidemiologic
477 research; and 4) medical economics research.

478

479 The most recent revision of the system, ICD-10, implemented in October 2015, provides more
480 than 14,400 different codes and can be expanded to over 16,000 codes by using optional sub-
481 classifications. It is not possible to convert ICD-9 datasets to ICD-10. In the ICD-10 coding
482 system, characters 1-3 indicate the category of disease; 4-6 indicate etiology, anatomic site,
483 severity or other clinical detail of disease; and character 7 is a placeholder for extending the code
484 to increase specificity. The designation “E” indicates endocrine, nutritional and metabolic
485 diseases, while “J” applies to diseases of the respiratory system.

486

487 Some CF specialists were engaged in the ICD-10 development process but the degree of
488 influence was limited, and coding for diseases or disorders caused by CFTR dysfunction is not
489 ideal, including the absence of a code for CFTR-related disorder (CFTR-RD). The current ICD-
490 10 code is undergoing revision to ICD-11, which is due to be completed in 2018. Participation is
491 invited (<http://www.who.int/classifications/icd/revision/en/>), and we encourage involvement by
492 CF caregivers.

493

494 A list of ICD-10 codes that should be used in the delivery of care for those disorders associated
495 with *CFTR* mutations (that is, CF, CRMS/CFSPID, and CFTR-related disorder) is shown in
496 Table II.

497

498 **CONCLUSION**

499

500 Although newborn screening is now widely implemented, the diagnosis of CF is not always
501 clear. A sweat test is required for confirmation of CF; a sweat chloride level ≥ 60 mmol/L
502 indicates a diagnosis of CF and a sweat chloride level < 30 mmol/L indicates that CF is unlikely.
503 In individuals who fall into the intermediate sweat chloride level, 30-59 mmol/L, genetic
504 analysis is required. Further testing for CFTR function such as NPD and ICM may also be
505 indicated but need to be performed in a specialized center approved for such studies. Some
506 individuals with sweat chloride levels from 30-59 mmol/L or even ≤ 29 mmol/L and
507 inconclusive genetic testing may also be designated as CRMS/CFSPID due to the results of
508 NBS, but further research is needed to determine their prognosis, best practice, and frequency of
509 follow-up.

510

511 **Table I: Consensus Recommendations for Diagnosis of Cystic Fibrosis**

	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 weeks of corrected gestational age.	87%	0
3	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).	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 of less than 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 less than 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 [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis: <ul style="list-style-type: none"> • CF-causing mutation: Individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed) 	100%	0

	<ul style="list-style-type: none"> • Mutation of varying clinical consequence (MVCC): a mutation that in combination with a CF-causing mutation or another MVCC mutation may result in CF • Uncharacterized mutation/mutation of unknown clinical consequence (UNK): mutations that have not been evaluated by CFTR2 and may be disease-causing or of variable clinical consequences or benign • Non-CF causing mutation: individuals with 1 or more are unlikely to have CF (as a result of that allele) 		
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 CFTR 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 Therapeutics Development Network (TDN) or ECFS Clinical Trial Network (CTN).	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 CFTR dysfunction (a sweat chloride \geq 60 mmol/L or CF-typical NPD or ICM).	93%	0
16	The term CRMS is used in U.S. for health care 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 screen- positive individuals 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"> • A sweat chloride value less than 30 mmol/L and 2 <i>CFTR</i> mutations, at least 1 of which has unclear phenotypic consequences OR <ul style="list-style-type: none"> • An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations 	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	<i>Research Recommendation:</i> 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, since these terms have no harmonized definition and could be confusing for families or caregivers.	83%	1

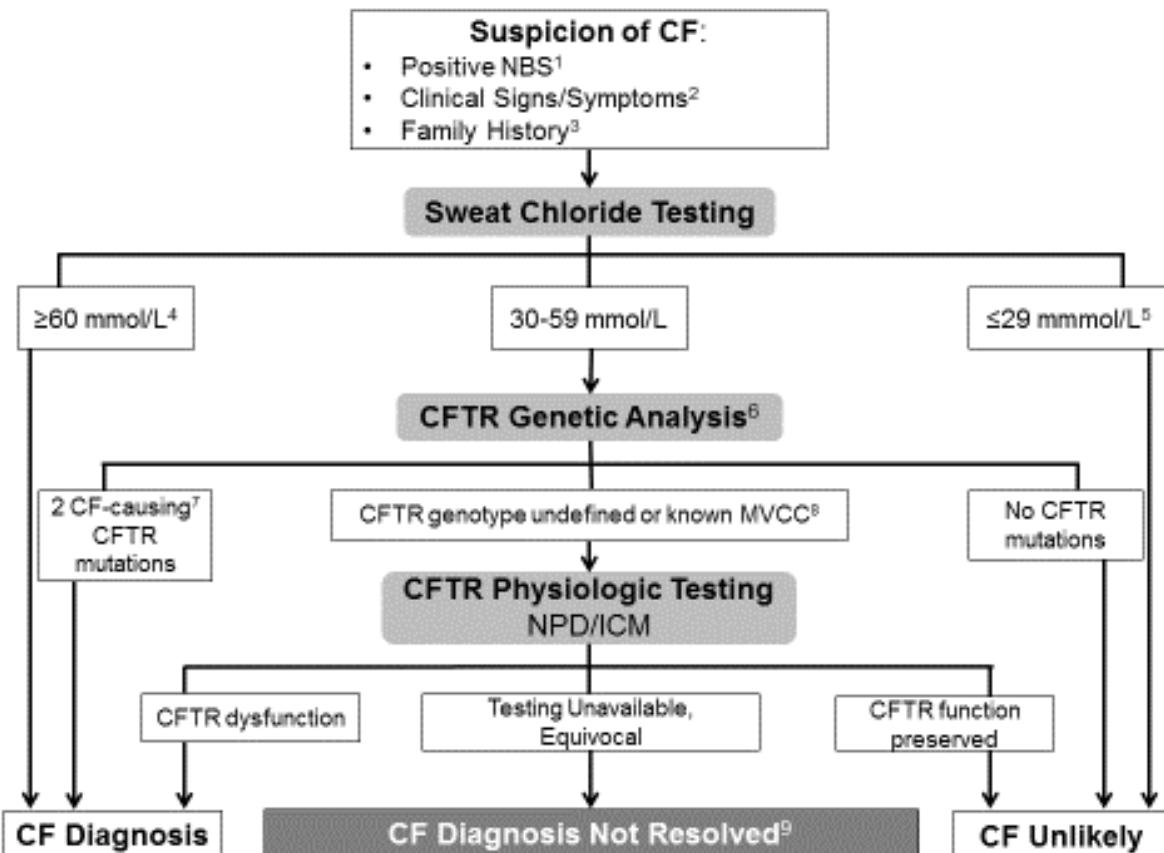
512

513 **TABLE II. ICD-10 Codes for Use in Individuals with Cystic Fibrosis and other CFTR**
 514 **Dysfunctional Diseases or Disorders.**

Disease/Disorder	Primary ICD-10 Code	Secondary ICD-10 Code
Cystic fibrosis, unspecified	E84.9	
Cystic fibrosis, with meconium ileus	E84.11	
Cystic fibrosis, with other intestinal manifestations (eg, distal intestinal obstruction syndrome (DIOS))	E84.19	
Cystic fibrosis, with pulmonary manifestations	E84.0	Use secondary code for details such as infectious organisms present (eg, B96.5 for <i>Pseudomonas aeruginosa</i>)
Cystic fibrosis, with acute pneumothorax	E84.09	J93.83
Cystic fibrosis, with pneumothorax not otherwise specified	E84.09	J93.9
Cystic fibrosis, 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 CBAVD Bronchiectasis, chronic acquired	K85.9 Q55.4** J47.9	Z14.1 (Cystic fibrosis carrier status)

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

517 **Preferred over N46.025 (azoospermia due to a systemic disease)



518

519 **Figure. Recommended Pathway for Diagnosis of Cystic Fibrosis.**

520 Notes:

- 521 1. A positive newborn screen may include *CFTR* genetic analysis. (See also Addendum for J Pediatrics MS #4,
 522 which is being drafted.) Even though the genetic analysis may be done first, to establish the diagnosis of CF, sweat
 523 chloride testing is the first test to be considered.
- 524 2. Clinical symptoms refer to nonscreened patients. (See also Addendum for J Pediatrics MS #6.)
- 525 3. Family history refers to a 1st degree relative with CF (parent, child, sibling).
- 526 4. All individuals with a CF diagnosis should undergo genotyping.
- 527 5. Rare individuals may have CF with a sweat chloride below the intermediate range.⁽¹⁹⁾ CF may still be considered
 528 as a diagnosis if alternatives are excluded and other confirmatory tests (genotype, physiologic testing) support CF.
 529 (See also Addendum for J Pediatrics MS #3).
- 530 6. CF-causing as defined by CFTR2 group.⁽¹⁹⁾ For further details and discussion see Addendum for J Pediatrics MS
 531 #3.
- 532 7. Genetic analysis that reveals *CFTR* variants, but cannot be classified as a CF-causing genotype. If genetic analysis
 533 is limited, and especially if only one *CFTR* variant is identified, further *CFTR* testing (such as sequencing,
 534 deletion/duplication detection) should be performed. (See also Addendum for J Pediatrics MS #3.)
- 535 8. The absence of any CF-causing mutation, or mutation of varying clinical consequence (MVCC), or undefined
 536 *CFTR* variants makes CF unlikely. Variants that are known to be non-CF-causing are not considered to be CFTR
 537 variants for purposes of diagnosis.
- 538 9. CF diagnosis not resolved is meant to consider alternative characterizations such as CRMS/CFSPID in the case of
 539 NBS; CFTR-related disorder in appropriate circumstances. In many instances no distinct label may be appropriate,
 540 but further follow-up may be warranted. In these cases, the use of "CF carrier" or the specific clinical problem
 541 should be used for characterization/labeling purposes.

542

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787 **ADDENDUM 1**

788

789 References to manuscripts being drafted for submission to *The Journal of Pediatrics* as part of
790 the supplement entitled "*Diagnosis of Cystic Fibrosis: Consensus Guidelines and Supporting*
791 *Evidence from the Cystic Fibrosis Foundation 2015 Diagnosis Consensus Conference.*" (Titles
792 and authorship may not be final; responsible authors are denoted in bold type.)

793

794 MS # 1. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation
795 (this manuscript)

796

797 MS # 2. Cystic Fibrosis Diagnostic Challenges over Four Decades: Historical Perspectives and
798 Lessons Learned

799 (**P. Farrell**, T. White, B. Rosenstein and N. Derichs)

800

801 MS # 3. Applying *CFTR* Genetics and CFTR2 Data to Facilitate Diagnoses
802 (**P. Sosnay**, C. Castellani and D. Salinas)

803

804 MS # 4. Diagnosis of Cystic Fibrosis in Screened Populations

805 (**P. Farrell**, T. White, M. Howenstine, A. Munck, R. Parad, M. Rosenfeld, O. Sommerberg, F.
806 Accurso, and J. Davies)

807

808 MS # 5. CFTR-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive
809 Diagnosis

810 (**C. Ren**, K. Southern, M. Howenstine, A. Munck, I. Sermet, and D. Borowitz)

811

812 MS # 6. Diagnosis of Cystic Fibrosis in Nonscreened Populations

813 (**P. Sosnay**, N. Derichs, and J. Nick)

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816 **ADDENDUM 2** [revisions to the 2008 consensus guidelines for diagnosis]:

- 817 • Sweat testing should be done in everyone, including all NBS+ infants
- 818 • Sweat Cl normal threshold is 30 mmol/L for all ages
- 819 • NPD/ICM should be done in a validated lab
- 820 • Use the CFTR2 classification of CFTR mutations
- 821 • CRMS=CFSPID → Harmonized definition
- 822 • Presumptive Dx of CF can be made in NBS+/2 mutation infant
- 823 • Non screened population with non-diagnostic sweat Cl
 - 824 ○ Extended genetic analysis
 - 825 ○ Ancillary testing NPD/ICM
- 826 • CRMS/CFSPID
 - 827 ○ Repeat sweat testing up to 2 y/o
 - 828 ○ Extended genetic analysis is recommended

- 829 ○ Duration and frequency of follow up remains undetermined
830 ○ Conversion to a CF Dx is a clinical decision
- 831 • Other definitions
- 832 ○ Avoid terms like “atypical” or “nonclassical” CF since there is no consensus
833 definition of these terms
- 834 ○ CFTR Related Disorder: A monosymptomatic entity that does not meet diagnostic
835 criteria for CF

DRAFT