INSTRUCTIONS:

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

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

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

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

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

by

Philip M. Farrell, MD, PhD, et al

Philip M. Farrell, MD, PhD
Emeritus Dean and Professor
Departments of Pediatrics and Population Health Sciences
University of Wisconsin School of Medicine and Public Health
Clinical Sciences Center, K4/948
600 Highland Avenue
Madison WI 53792

Name, address, e-mail address, telephone/fax numbers of corresponding author:

Philip M. Farrell, MD, PhD
University of Wisconsin School of Medicine and Public Health
Clinical Sciences Center, K4/948
600 Highland Avenue
Madison WI 53792
pmfarrell@wisc.edu
Phone: 608-263-8555 Fax: 608-263-0510

Notation of no reprints

List of key words not in the title: newborn screening, CFTR-related metabolic syndrome, CF-screen positive, inconclusive diagnosis, immunoreactive trypsinogen, pancreatitis associated protein, sweat test, nasal potential difference, intestinal current measurement

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

Funded by the Cystic Fibrosis Foundation. Conflicts of interest:

ABSTRACT

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

Methods: 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 ≥80% affirmative votes was required for acceptance of each 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 another 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 CFTR2 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 (CRMS) or CF Screen Positive, Inconclusive Diagnosis (CFSPID); these terms are now merged and equivalent, and CRMS/CFSPID may be used. ICD-10 codes for use in diagnoses associated with *CFTR* mutations are included.

250/250 words

INTRODUCTION

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

A diagnosis of CF initially relied on phenotype, with clinical recognition of characteristic signs and symptoms.[8] (See also Addendum for J Pediatrics Manuscript (MS) #6, which is being drafted.) However, due to widespread CF newborn screening (NBS), at least 64% of new CF diagnoses in the United States now occur in asymptomatic or minimally symptomatic infants following a positive NBS result.[9] Although the majority of these screen-positive infants can be readily diagnosed with CF after a confirmatory test showing high sweat chloride concentration, the diagnosis is not clear in some individuals,[10,11] leading to persistent challenges[12] and stresses, and importantly including a potentially disturbed parent/child relationship.[13–15] Furthermore, universal NBS was implemented only recently in the United States, and many individuals born there 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 as a result of CFTR dysfunction can be highly variable. Symptoms can include subtle presentations of pancreatitis or respiratory symptoms in older children and adults, nasal polyposis, and male infertility).[16–18] (See also Addendum for J Pediatrics MS #6, which is being drafted.)

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 of these patients. International collection of clinical data from individuals with CF[19] and laboratory advances[20] provide functional insight into the physiological impact of the most common mutations (see Addendum for J Pediatrics MS #3, which is being drafted). Due to this new information, and to seek harmony with the diagnostic criteria and terminology[21] of the European Cystic Fibrosis Society

(ECFS), it was decided that the 2008 diagnostic guidelines[22] of the Cystic Fibrosis Foundation (CF Foundation) should be revised.

The CF Foundation convened a committee of 32 experts in the diagnosis of CF from nine countries 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)[23] or CF Screen Positive, Inconclusive Diagnosis (CFSPID),[24] and CFTR-related disorder.[25] The recommendations in this document address individuals with both clear and unclear diagnosis, including infants with positive NBS and/or prenatal diagnosis (see Addendum for J Pediatrics MS #4, which is being drafted), and individuals with CF-like symptoms who were either never screened or who had false negative newborn or prenatal screening results (see Addendum for J Pediatrics MS #6, which is being drafted). Case studies, designed to show how the recommendations should be applied in challenging clinical scenarios, can be found in additional manuscripts created as a result of this conference, published as Supplement X of *The Journal of Pediatrics* (see Addendum for J Pediatrics MS #3-#6).

METHODS

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

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

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

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

RESULTS AND DISCUSSION

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

The committee approved 27 consensus statements (**Table I**) in 4 overlapping categories that apply to:

1. Both screened and nonscreened populations;
2. Screened pediatric populations, ie, fetuses undergoing prenatal testing and neonates;
3. Infants with uncertain diagnosis and designated either CRMS or CFSPID (now considered to be the same)
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 individuals.

The **Figure** provides a simplified algorithm for how these consensus statements should be applied to individuals under suspicion of CF. 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 demonstration of abnormal CFTR function by measurement of chloride concentration in the sweat.[22] 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.[27–30] Following the committee's recommendations, shown below, will improve reliability of the result.

1. All Populations: Sweat chloride testing should be performed according to approved procedural guidelines published in established, international protocols such as the CLSI 2009 Guidelines.

Following appropriate protocols for performing the sweat test[28] is important for achieving accurate results and minimizing collection of inadequate amounts of sweat (quantity not sufficient, QNS).[29–33] (See also Addendum for J Pediatrics MS #4, which is being drafted.)

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 of corrected gestational age.

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

<u>3. For Newborns:</u> 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).

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

<u>4. For Newborns:</u> 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.[39] The CF Foundation recommends that infants with CF have an initial visit at an accredited CF care center within 24-72 hours of diagnosis,[39] 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:

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

However, definitive diagnosis requires demonstration of CFTR dysfunction.

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.[40–43] A second, confirmatory, sweat test is not necessary, nor is it likely to be reimbursable; this is a change from previous CF Foundation diagnostic guidelines.[22,44]

SWEAT CHLORIDE TEST RESULTS ≥ 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 ≥ 60 mmol/L.

While 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 screening procedures and not diagnostic studies. The genetic analysis included as part of many NBS programs must not be relied upon for conclusive diagnosis, as errors can arise from problems with the Guthrie card,[45] changes in the mutation panel utilized by the NBS program (for example, see ref. 46), or detection of 2 *CFTR* mutations in *cis* (ie, on the same chromosome).[47] (See also Addendum for J Pediatrics MS #3, which is being drafted.)

7. For Newborns: Individuals who are 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. The screening result should be confirmed in a clinical genetics laboratory, even if a sweat chloride result is positive. The genetic testing results now have additional value in therapy selection.[48]

SWEAT CHLORIDE TEST RESULTS ≤ 29 MMOL/L

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

9. All Populations: 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 *CFTR* genotyping support CF and not an alternative diagnosis.

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

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

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 two 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.[11,51,52] Evidence may be provided by *CFTR* genotype.[19] (See Addendum for J Pediatrics MS #3, which is being drafted to discuss *CFTR* genetic testing and interpretation in detail) or by further CFTR physiologic testing.[53–56] For discussion of demonstration of CFTR dysfunction including the use of nasal potential difference (NPD) or intestinal current measurement (ICM) on the screen-positive newborn see Addendum for J Pediatrics MS #4, which is being drafted; see MS #6 for information on the symptomatic patient).

NEXT STEPS FOR INTERMEDIATE SWEAT TEST RESULTS

11. All Populations: The latest classifications identified in the CFTR2 project [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis:

- **CF-causing mutation: Individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed)**
- **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): mutation that has 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)**

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

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.

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 a normal sweat chloride.[49,50] (See Addendum for J Pediatrics MS #3, which is being drafted, for further exploration of this topic).

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 CF in whom 2 *CFTR* mutations have not been detected. Thus, while 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. (See Addendum for J Pediatrics Manuscripts #3, #5, and #6, being drafted for more in-depth discussion.)

To further explore 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. Clinical electrophysiological tests that directly measure CFTR function, such as NPD and ICM may be useful to confirm a diagnosis of CF.[57]

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 (TDN) or ECFS Clinical Trial Network (CTN).

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

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 ≥ 60 mmol/L or CF-typical NPD or ICM).

FOR THE NEWBORN WITH AN INCONCLUSIVE DIAGNOSIS

16. For Newborns: The term CRMS is used in the United States for health care 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 labelled either CRMS[23] or CFSPID.[24] (See also Addendum for J Pediatrics MS #5, which is being drafted.) 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 ICD-10 code P09. However, due to US health care system requirements (see Addendum for J Pediatrics MS #2, which is being drafted), CRMS (ICD-10 code E88.89) must be used in clinical settings of the USA for continuing, follow-up care. These two terms are nearly identical, and the Consensus Committee recommends that the two 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.[65]

17. For Newborns: The term CRMS/CFSPID is reserved for screen-positive individuals 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 (see Addendum for J Pediatrics MS #6, which is being drafted).

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

- **A sweat chloride value less than 30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences**

OR

- **An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations**

Individuals designated as CRMS/CFSPID should be seen 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.[23,66]

NEXT STEPS IN THE NEWBORN WITH CRMS/CFSPID DESIGNATION

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

19. For Newborns: 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.

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

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.

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.

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.[23,24] (See also Addendum for J Pediatrics MS #5, which is being drafted.) Monitoring symptoms, surveillance evaluations (respiratory tract cultures, imaging, and spirometry or lung-clearance index when age-appropriate), and measuring fecal elastase levels or following IRT or

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

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.

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.[23,24]

24. For Newborns, 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.

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. 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 pre-test probability 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
- The presence of 2 CF-causing *CFTR* mutations

  OR
- Physiologic testing demonstrating CFTR dysfunction.

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

FOR THE NONSCREENED INDIVIDUAL WITH THE 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. Though 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 [CBAVD/pancreatitis/bronchiectasis] associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF.

Individuals with a monosymptomatic CFTR-related disorder[25] should be assessed and followed by a CF physician. (See Addendum for J Pediatrics MS #6, which is being drafted.)

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.

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.

ICD-10 CODES FOR INDIVIDUALS WITH CFTR DYSFUNCTION

The International Statistical Classification of Diseases and Related Health Problems (ICD)[71] system is a medical classification list created collaboratively by the World Health Organization (WHO) 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."[72] 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 United States 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.

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 sub-classifications. It is not possible to convert ICD-9 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, while "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 (CFTR-RD). The current ICD-10 code is undergoing revision to ICD-11, 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.

CONCLUSION

Although newborn screening 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 ≥ 60 mmol/L indicates a diagnosis of CF and a sweat chloride level < 30 mmol/L indicates 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 need to be performed in a specialized center approved for such studies. Some individuals with sweat chloride levels from 30-59 mmol/L or even ≤ 29 mmol/L and inconclusive genetic testing may also be designated as CRMS/CFSPID due to the results of NBS, but further research is needed to determine their prognosis, best practice, and frequency of follow-up.

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 ≥ 60 mmol/L.	93%	0
7	Individuals who are 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.	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 *CFTR* 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 *CFTR* gene analysis and/or CFTR 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: • CF-causing mutation: Individuals with 2 copies on separate alleles will likely have CF (clinical sweat confirmation needed)	100%	0

	• 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 *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).	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: • A sweat chloride value less than 30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences OR • An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations	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 *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.	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 CFTR (sweat chloride, and possibly NPD/ICM), *CFTR* 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, *CFTR* genetic analysis, and CFTR functional testing should be used to confirm a CF diagnosis.	93%	0
26	The diagnosis of CFTR-related disorder has been defined as a monosymptomatic clinical entity [CBAVD/pancreatitis/bronchiectasis] associated with CFTR 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

TABLE II. ICD-10 Codes for Use in Individuals with Cystic Fibrosis and other CFTR 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 *Pseudomonas aeruginosa*)
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	K85.9	} Z14.1 (Cystic fibrosis carrier status)
CBAVD	Q55.4**	
Bronchiectasis, chronic acquired	J47.9	

*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

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

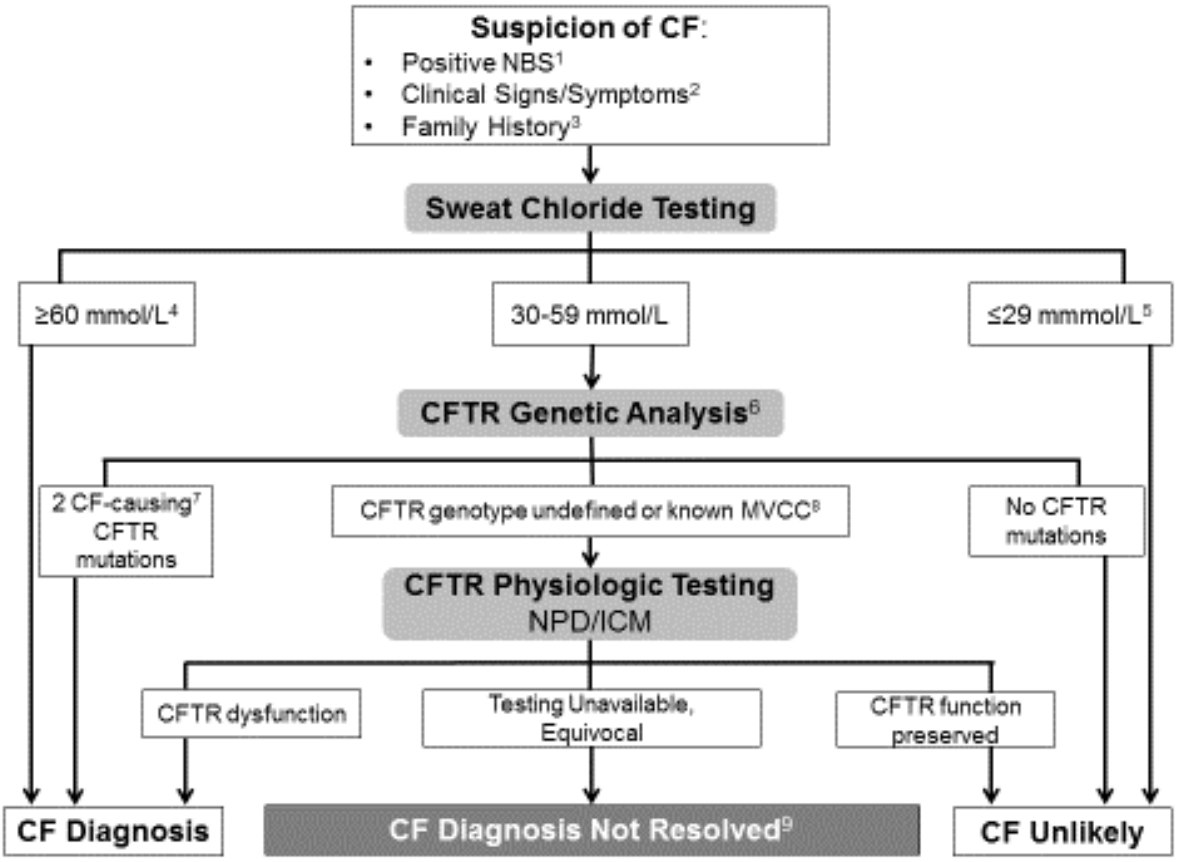

Figure. Recommended Pathway for Diagnosis of Cystic Fibrosis.

Notes:

1. A positive newborn screen may include *CFTR* genetic analysis. (See also Addendum for J Pediatrics MS #4, which is being drafted.) Even though the genetic analysis may be done first, to establish the diagnosis of CF, sweat chloride testing is the first test to be considered.
2. Clinical symptoms refer to nonscreened patients. (See also Addendum for J Pediatrics MS #6.)
3. Family history refers to a 1st degree relative with CF (parent, child, sibling).
4. All individuals with a CF diagnosis should undergo genotyping.
5. Rare individuals may have CF with a sweat chloride below the intermediate range.(19) CF may still be considered as a diagnosis if alternatives are excluded and other confirmatory tests (genotype, physiologic testing) support CF. (See also Addendum for J Pediatrics MS #3).
6. CF-causing as defined by CFTR2 group.(19) For further details and discussion see Addendum for J Pediatrics MS #3.
7. Genetic analysis that reveals *CFTR* variants, but cannot be classified as a CF-causing genotype. If genetic analysis is limited, and especially if only one *CFTR* variant is identified, further *CFTR* testing (such as sequencing, deletion/duplication detection) should be performed. (See also Addendum for J Pediatrics MS #3.)
8. The absence of any CF-causing mutation, or mutation of varying clinical consequence (MVCC), or undefined *CFTR* variants makes CF unlikely. Variants that are known to be non-CF-causing are not considered to be CFTR variants for purposes of diagnosis.
9. CF diagnosis not resolved is meant to consider alternative characterizations such as CRMS/CFSPID in the case of NBS; CFTR-related disorder in appropriate circumstances. In many instances 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.

ACKNOWLEDGEMENTS

Committee and Conference Chairs:

Philip Farrell, MD, PhD

Clement Ren, MD

Patrick Sosnay, MD

Executive Committee:

Frank Accurso, MD

Nico Derichs, MD

Michelle Howenstine, MD

Susanna McColley, MD

Michael Rock, MD

Margaret Rosenfeld, MD, MPH

Isabelle Sermet-Gaudelus, MD, PhD

Kevin Southern, PhD

Sarah Hempstead, MS

Terry White, PhD

Conference Committee:

Hannah Blau, MD

Drucy Borowitz, MD

Preston Campbell III, MD

Carlo Castellani, MD

Jane Davies, MD

Kris De Boeck, PhD

Silvia Gartner, MD, PhD

Tanja Gonska, MD

Tyler Groves, MBBS

Hara Levy, MD, MMSc

Bruce Marshall, MD

John Massie, FRACP
Carlos Milla, MD
Mark Montgomery, MD
Anne Munck, MD
Jerry Nick, MD
Richard Parad, MD, MPH
Beryl Rosenstein, MD
Danieli Salinas, MD
Don B Sanders, MD, MS
Olaf Sommerburg, MD
Robert Wilmott, MD
Michael Wilschanski, MBBS

REFERENCES

1. Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. Stat Med. 1996 Mar 15;15(5):449–62.

2. Palomaki GE, FitzSimmons SC, Haddow JE. Clinical sensitivity of prenatal screening for cystic fibrosis via CFTR carrier testing in a United States panethnic population. Genet Med Off J Am Coll Med Genet. 2004 Oct;6(5):405–14.

3. Hamosh A, FitzSimmons SC, Macek M, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr. 1998 Feb;132(2):255–9.

4. ECFS Patient Registry - ECFSPR_Report2013_02.2016.pdf [Internet]. [cited 2016 May 9]. Available from: https://www.ecfs.eu/sites/default/files/images/ECFSPR_Report2013_02.2016.pdf

5. Burgel P-R, Bellis G, Olesen HV, Viviani L, Zolin A, Blasi F, et al. Future trends in cystic fibrosis demography in 34 European countries. Eur Respir J. 2015 Jul;46(1):133–41.

6. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science. 1989 Sep 8;245(4922):1073–80.

7. Cystic Fibrosis Mutation Database [Internet]. [cited 2016 May 3]. Available from: http://www.genet.sickkids.on.ca/cftr/app

8. Report of the committe for a study for evaluation of testing for cystic fibrosis. J Pediatr. 1976 Apr;88(4 Pt 2):711–50.

9. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry 2014 Annual Data Report. Bethesda, MD; 2015.

10. Ren CL, Fink AK, Petren K, Borowitz DS, McColley SA, Sanders DB, et al. Outcomes of infants with indeterminate diagnosis detected by cystic fibrosis newborn screening. Pediatrics. 2015 Jun;135(6):e1386-1392.

11. Parad RB, Comeau AM. Diagnostic dilemmas resulting from the immunoreactive trypsinogen/DNA cystic fibrosis newborn screening algorithm. J Pediatr. 2005 Sep;147(3 Suppl):S78-82.

12. Levy H, Farrell PM. New challenges in the diagnosis and management of cystic fibrosis. J Pediatr. 2015 Jun;166(6):1337–41.

13. Tluczek A, Chevalier McKechnie A, Lynam PA. When the cystic fibrosis label does not fit: a modified uncertainty theory. Qual Health Res. 2010 Feb;20(2):209–23.

14. Tluczek A, Orland KM, Cavanagh L. Psychosocial consequences of false-positive newborn screens for cystic fibrosis. Qual Health Res. 2011 Feb;21(2):174–86.

15. Nelson MR, Adamski CR, Tluczek A. Clinical practices for intermediate sweat tests following abnormal cystic fibrosis newborn screens. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2011 Dec;10(6):460–5.

16. Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. Chest. 2004 Oct;126(4):1215–24.

17. Masaryk TJ, Achkar E. Pancreatitis as initial presentation of cystic fibrosis in young adults. A report of two cases. Dig Dis Sci. 1983 Oct;28(10):874–8.

18. Marshak T, Rivlin Y, Bentur L, Ronen O, Uri N. Prevalence of rhinosinusitis among atypical cystic fibrosis patients. Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg. 2011 Apr;268(4):519–24.

19. CFTR2@Johns Hopkins - Home Page [Internet]. [cited 2016 May 3]. Available from: http://cftr2.org/

20. Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nat Genet. 2013 Oct;45(10):1160–7.

21. Ooi CY, Dupuis A, Ellis L, Jarvi K, Martin S, Gonska T, et al. Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language? Thorax. 2012 Jul;67(7):618–24.

22. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008 Aug;153(2):S4–14.

23. Cystic Fibrosis Foundation, Borowitz D, Parad RB, Sharp JK, Sabadosa KA, Robinson KA, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. J Pediatr. 2009 Dec;155(6 Suppl):S106-116.

24. Munck A, Mayell SJ, Winters V, Shawcross A, Derichs N, Parad R, et al. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): A new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2015 Nov;14(6):706–13.

25. Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2011 Jun;10 Suppl 2:S86-102.

26. SurveyMonkey: Free online survey software & questionnaire tool [Internet]. [cited 2016 May 3]. Available from: https://www.surveymonkey.com./

27. Rock M, Farrell P. Sweat testing after abnormal CF newborn screening: a single center 20 year experience [abstract]. Pediatr Pulmonol. 50(S41):381.

28. LeGrys VA, Applequist R, Briscoe D, Farrell P, Hickstein R, Lo S, et al. Sweat testing: Sample collection and quantitative chloride analysis. Approved guideline, 3rd edition. CLSI Document C34-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

29. LeGrys VA, Yankaskas JR, Quittell LM, Marshall BC, Mogayzel PJ, Cystic Fibrosis Foundation. Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. J Pediatr. 2007 Jul;151(1):85–9.

30. Legrys VA, McColley SA, Li Z, Farrell PM. The need for quality improvement in sweat testing infants after newborn screening for cystic fibrosis. J Pediatr. 2010 Dec;157(6):1035–7.

31. McColley SA, Shryock H, Healy E, Nash C. Improving sweat test QNS rates for infants with positive CF NBS in Illinois [abstract]. Pediatr Pulmonol. 47(S35):382.

32. Abdulhamid I, Schuen J, Gregoire-Bottex M. Reducing the rate of inadequate sweat testing for NBS in the state of Michigan [abstract]. Pediatr Pulmonol. 2013;48(S36):377.

33. Aqil B, West A, Dowlin M, Tam E, Nordstrom C, Buffone G, et al. Implementation of a quality improvement program to improve sweat test performance in a pediatric hospital. Arch Pathol Lab Med. 2014 Jul;138(7):920–2.

34. Eng W, LeGrys VA, Schechter MS, Laughon MM, Barker PM. Sweat-testing in preterm and full-term infants less than 6 weeks of age. Pediatr Pulmonol. 2005 Jul;40(1):64–7.

35. Guimarães EV, Schettino GCM, Camargos PAM, Penna FJ. Prevalence of hyponatremia at diagnosis and factors associated with the longitudinal variation in serum sodium levels in infants with cystic fibrosis. J Pediatr. 2012 Aug;161(2):285–9.

36. Neville LA, Ranganathan SC. Vitamin D in infants with cystic fibrosis diagnosed by newborn screening. J Paediatr Child Health. 2009 Feb;45(1–2):36–41.

37. Giglio L, Candusso M, D'Orazio C, Mastella G, Faraguna D. Failure to thrive: the earliest feature of cystic fibrosis in infants diagnosed by neonatal screening. Acta Paediatr Oslo Nor 1992. 1997 Nov;86(11):1162–5.

38. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2016 Mar;15(2):147–57.

39. Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009 Dec;155(6 Suppl):S73-93.

40. Tluczek A, Koscik RL, Farrell PM, Rock MJ. Psychosocial risk associated with newborn screening for cystic fibrosis: parents' experience while awaiting the sweat-test appointment. Pediatrics. 2005 Jun;115(6):1692–703.

41. Ulph F, Cullinan T, Qureshi N, Kai J. Parents' responses to receiving sickle cell or cystic fibrosis carrier results for their child following newborn screening. Eur J Hum Genet EJHG. 2015 Apr;23(4):459–65.

42. Comeau AM, Accurso FJ, White TB, Campbell PW, Hoffman G, Parad RB, et al. Guidelines for implementation of cystic fibrosis newborn screening programs: Cystic Fibrosis Foundation workshop report. Pediatrics. 2007 Feb;119(2):e495-518.

43. Tluczek A, Koscik RL, Modaff P, Pfeil D, Rock MJ, Farrell PM, et al. Newborn screening for cystic fibrosis: parents' preferences regarding counseling at the time of infants' sweat test. J Genet Couns. 2006 Aug;15(4):277–91.

44. Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr. 1998 Apr;132(4):589–95.

45. Therrell BL, Hannon WH, Hoffman G, Ojodu J, Farrell PM. Immunoreactive Trypsinogen (IRT) as a Biomarker for Cystic Fibrosis: challenges in newborn dried blood spot screening. Mol Genet Metab. 2012 May;106(1):1–6.

46. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6(5):387–91.

47. Cordovado SK, Hendrix M, Greene CN, Mochal S, Earley MC, Farrell PM, et al. CFTR mutation analysis and haplotype associations in CF patients. Mol Genet Metab. 2012 Feb;105(2):249–54.

48. Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. Lancet Respir Med. 2013 Apr;1(2):158–63.

49. Augarten A, Kerem BS, Yahav Y, Noiman S, Rivlin Y, Tal A, et al. Mild cystic fibrosis and normal or borderline sweat test in patients with the 3849 + 10 kb C-->T mutation. Lancet Lond Engl. 1993 Jul 3;342(8862):25–6.

50. Highsmith WE, Burch LH, Zhou Z, Olsen JC, Boat TE, Spock A, et al. A novel mutation in the cystic fibrosis gene in patients with pulmonary disease but normal sweat chloride concentrations. N Engl J Med. 1994 Oct 13;331(15):974–80.

51. Stewart B, Zabner J, Shuber AP, Welsh MJ, McCray PB. Normal sweat chloride values do not exclude the diagnosis of cystic fibrosis. Am J Respir Crit Care Med. 1995 Mar;151(3 Pt 1):899–903.

52. Feldmann D, Couderc R, Audrezet M-P, Ferec C, Bienvenu T, Desgeorges M, et al. CFTR genotypes in patients with normal or borderline sweat chloride levels. Hum Mutat. 2003 Oct;22(4):340.

53. Goubau C, Wilschanski M, Skalická V, Lebecque P, Southern KW, Sermet I, et al. Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. Thorax. 2009 Aug;64(8):683–91.

54. Naehrlich L, Ballmann M, Davies J, Derichs N, Gonska T, Hjelte L, et al. Nasal potential difference measurements in diagnosis of cystic fibrosis: an international survey. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2014 Jan;13(1):24–8.

55. Hirtz S, Gonska T, Seydewitz HH, Thomas J, Greiner P, Kuehr J, et al. CFTR Cl- channel function in native human colon correlates with the genotype and phenotype in cystic fibrosis. Gastroenterology. 2004 Oct;127(4):1085–95.

56. Derichs N, Sanz J, Von Kanel T, Stolpe C, Zapf A, Tümmler B, et al. Intestinal current measurement for diagnostic classification of patients with questionable cystic fibrosis: validation and reference data. Thorax. 2010 Jul;65(7):594–9.

57. Ooi CY, Dupuis A, Gonska T, Ellis L, Ni A, Jarvi K, et al. Does integration of various ion channel measurements improve diagnostic performance in cystic fibrosis? Ann Am Thorac Soc. 2014 May;11(4):562–70.

58. Wilschanski M. The use of NPD for confirming CF diagnoses with and without screening results: Can it resolve diagnostic dilemmas in infants. CF Diagnosis Consensus ConferenceThorax. 2010 Jun;65(6):539-44.; 2015 Oct 6; Phoenix, AZ.

59. Sermet-Gaudelus I, Girodon E, Roussel D, Deneuville E, Bui S, Huet F, et al. Measurement of nasal potential difference in young children with an equivocal sweat test following newborn screening for cystic fibrosis. Thorax. 2010 Jun;65(6):539–44.

60. De Boeck K, Kent L, Davies J, Derichs N, Amaral M, Rowe SM, et al. CFTR biomarkers: time for promotion to surrogate end-point. Eur Respir J. 2013 Jan;41(1):203–16.

61. Bagheri-Hanson A, Nedwed S, Rueckes-Nilges C, Naehrlich L. Intestinal current measurement versus nasal potential difference measurements for diagnosis of cystic fibrosis: a case-control study. BMC Pulm Med. 2014;14:156.

62. De Jonge HR, Ballmann M, Veeze H, Bronsveld I, Stanke F, Tümmler B, et al. Ex vivo CF diagnosis by intestinal current measurements (ICM) in small aperture, circulating Ussing chambers. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2004 Aug;3 Suppl 2:159–63.

63. De Boeck K, Derichs N, Fajac I, de Jonge HR, Bronsveld I, Sermet I, et al. New clinical diagnostic procedures for cystic fibrosis in Europe. J Cyst Fibros Off J Eur Cyst Fibros Soc. 2011 Jun;10 Suppl 2:S53-66.

64. Sermet-Gaudelus I. Can NPD resolve diagnostic dilemmas in difficult cases with and without screening results? CF Diagnosis Consensus Conference; 2015 Oct 6; Phoenix, AZ.

65. Castellani C, Massie J, Sontag M, Southern KW. Newborn screening for cystic fibrosis. Lancet Respir Med [Internet]. [cited 2016 May 5]; Available from: http://dx.doi.org/10.1016/S2213-2600(16)00053-9

66. Ooi CY, Castellani C, Keenan K, Avolio J, Volpi S, Boland M, et al. Inconclusive diagnosis of cystic fibrosis after newborn screening. Pediatrics. 2015 Jun;135(6):e1377-1385.

67. Levy H, Nugent M, Schneck K, Stachiw-Hietpas D, Laxova A, Lakser O, et al. Refining the continuum of CFTR-associated disorders in the era of newborn screening. Clin Genet. 2016 May;89(5):539–49.

68. Kharrazi M, Yang J, Bishop T, Lessing S, Young S, Graham S, et al. Newborn Screening for Cystic Fibrosis in California. Pediatrics. 2015 Dec;136(6):1062–72.

69. Rock MJ, Mischler EH, Farrell PM, Bruns WT, Hassemer DJ, Laessig RH. Immunoreactive trypsinogen screening for cystic fibrosis: characterization of infants with a false-positive screening test. Pediatr Pulmonol. 1989;6(1):42–8.

70. Massie J, Curnow L, Tzanakos N, Francis I, Robertson CF. Markedly elevated neonatal immunoreactive trypsinogen levels in the absence of cystic fibrosis gene mutations is not an indication for further testing. Arch Dis Child. 2006 Mar;91(3):222–5.

71. World Health Organization. Geneva: International Statistical Classification of Diseases and Related Health Problems [updated Feb 2016; cited 20 May 2016]. Available from http://apps.who.int/classifications/icd10/browse/2016/en.

72. World Health Organization. Geneva: International Classification of Diseases (ICD) Information Sheet [updated Feb 2016; cited 20 May 2016]. Available from http://www.who.int/classifications/icd/factsheet/en/.

ADDENDUM 1

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

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

MS # 2. Cystic Fibrosis Diagnostic Challenges over Four Decades: Historical Perspectives and Lessons Learned
(**P. Farrell**, T. White, B. Rosenstein and N. Derichs)

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

MS # 4. Diagnosis of Cystic Fibrosis in Screened Populations
(**P. Farrell,** T. White, M. Howenstine, A. Munck, R. Parad, M. Rosenfeld, O. Sommerberg, F. Accurso, and J. Davies)

MS # 5. CFTR-Related Metabolic Syndrome and Cystic Fibrosis Screen Positive, Inconclusive Diagnosis
(**C. Ren**, K. Southern, M. Howenstine, A. Munck, I. Sermet, and D. Borowitz)

MS # 6. Diagnosis of Cystic Fibrosis in Nonscreened Populations
(**P. Sosnay**, N. Derichs, and J. Nick)

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

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

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