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

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

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

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

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

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease in the US, affecting approximately 1 in 4000 newborns in the US,[1-3] and occurring at higher frequencies in some European countries.[4,5] CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (*CFTR*), which encodes an 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.[8,9] However, because of widespread CF newborn screening (NBS), at least 64% of new CF diagnoses in the US now occur in

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

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List of 2015 CF Foundation Diagnosis Consensus Conference Committee and Executive Subcommittee members is available at www.jpeds.com (**Appendix**).

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

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

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

Methods

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

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

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

Results

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

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

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