Diagnosis of Cystic Fibrosis in Nonscreened Populations

Patrick R. Sosnay, MD[1], Terry B. White, PhD[2], Philip M. Farrell, MD, PhD[3], Clement L. Ren, MD[4], Nico Derichs, MD[5], Michelle S. Howenstine, MD[4], Jerry A. Nick, MD[6], and Kris De Boeck, MD[7]

Objective Although the majority of cases of cystic fibrosis (CF) are now diagnosed through newborn screening, there is still a need to standardize the diagnostic criteria for those diagnosed outside of the neonatal period. This is because newborn screening started relatively recently, it is not performed everywhere, and even for individuals who were screened, there is the possibility of a false negative. To limit irreversible organ pathology, a timely diagnosis of CF and institution of CF therapies can greatly benefit these patients.

Study design Experts on CF diagnosis were convened at the 2015 CF Foundation Diagnosis Consensus Conference. The participants reviewed and discussed published works and instructive cases of CF diagnosis in individuals presenting with signs, symptoms, or a family history of CF. Through a modified Delphi methodology, several consensus statements were agreed upon. These consensus statements were updates of prior CF diagnosis conferences and recommendations.

Results CF diagnosis in individuals outside of newborn screening relies on the clinical evidence and on evidence of CF transmembrane conductance regulator (CFTR) dysfunction. Clinical evidence can include typical organ pathologies seen in CF such as bronchiectasis or pancreatic insufficiency but often represent a broad range of severity including mild cases. CFTR dysfunction can be demonstrated using sweat chloride testing, *CFTR* molecular genetic analysis, or CFTR physiologic tests. On the basis of the large number of patients with bona fide CF currently followed in registries with sweat chloride levels between 30 and 40 mmol/L, the threshold considered "intermediate" was lowered from 40 mmol/L in the prior diagnostic guidelines to 30 mmol/L. The CF diagnosis was also discussed in the context of CFTR-related disorders in which CFTR dysfunction may be present, but the individual does not meet criteria for CF.

Conclusions CF diagnosis remains a rare but important condition that can be diagnosed when characteristic clinical features are seen in an individual with demonstrated CFTR dysfunction. *(J Pediatr 2017;181S:S52-7).*

Since the identification of cystic fibrosis (CF) as a pathologic entity in 1938,[1] diagnosis has been based on the appearance of signs and symptoms of the disease. For many decades, diagnosis occurred in infancy or early childhood, although by the 1960s, the disease was occasionally being identified in adults,[2-4] who were usually pancreatic-sufficient. The identification of the gene for the CF transmembrane conductance regulator (*CFTR*) in 1989[5-7] and subsequent discovery of mutations that can alter quantity and/or function of the protein to varying degrees,[8] as well as the recognition of modifier genes,[9] have led to demonstration of a wider spectrum of CF in individuals of all ages and ethnicities.[10] It is now clear that in individuals with residual function *CFTR* mutations, clinical manifestation of CF may develop later in life.[11] Furthermore, although the advent of widespread newborn screening (NBS) has dramatically changed the diagnosis for many infants born in the last decade or so, more than one-third of all US diagnoses in 2014 were not a result of NBS.[12] Criteria to establish a diagnosis of CF outside of NBS are needed because CF NBS is neither universal nor foolproof; false negatives can and do occur.[12,13] Thus, although physicians today may have less clinical suspicion as a result of CF NBS, a diagnosis of CF or related entities must remain a consideration in anyone who displays signs and symptoms of the disease, regardless of age, race, or whether they may have undergone NBS.

Diagnosis of the Nonscreened Individual

The process for diagnosis of CF in individuals that present with clinical symptoms rather than a positive newborn screen does not differ greatly from that

CF	Cystic fibrosis
CFTR	CF transmembrane conductance regulator
CFTR2	Clinical and functional translation of CFTR
CT	Computed tomography
FEV_1	Forced expiratory volume in the first second
ICM	Intestinal current measurement
NBS	Newborn screening
NPD	Nasal potential difference

From the [1]Department of Medicine, Division of Pulmonary and Critical Care Medicine and McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Cystic Fibrosis Foundation, Bethesda, MD; [3]Departments of Pediatrics and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison WI; [4]Section of Pediatric Pulmonology, Allergy, and Sleep Medicine, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN; [5]CFTR Biomarker Center and Translational CF Research Group, CF Center, Pediatric Pulmonology and Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany; [6]Department of Medicine, National Jewish Health, Denver, CO; and [7]Pediatric Pulmonology, University Hospital of Leuven, University of Leuven, Leuven, Belgium

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Table I. 2015 CF Foundation diagnosis consensus conference recommendations related to diagnosis of CF in nonscreened populations*

Statement numbers*	Consensus statements	Comments
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.	This represents a change in the cut-offs for sweat chloride testing. In previous statements, an "unlikely CF" sweat chloride was <40 mmol/L;[19] at present it is <30 mmol/L. See "Change in Sweat Chloride Range Definitions" section.
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.	This draws on the international effort to characterize this clinical scenario. See "Alternative Diagnoses" section.
27	Clinicians should avoid the use of terms like classic/nonclassic CF, typical/atypical CF, delayed CF because these terms have no harmonized definition and could be confusing for families or caregivers.	The European CF Society Diagnostic Network Working Group has maintained a nonclassic or atypical CF label.[20,21] See "Alternative Diagnoses" section for discussion.

CBAVD, congenital bilateral absence of the vas deferens.
*Adapted from Farrell et al.[14]

recommended by earlier diagnosis consensus criteria[13] (flow chart representing the diagnostic process recommended for all populations by the 2015 CF diagnosis consensus committee[14]). There is growing recognition that CF can present at any age, and in any race or ethnicity. In making the diagnosis, an appropriate clinical presentation needs to be linked with evidence of CFTR dysfunction. Since earlier consensus statements, several advances have evolved our experience with both the clinical presentation (as we have recognized a broader spectrum of CF and CFTR-related disorders) and with our understanding of the molecular and cellular pathophysiology of CFTR dysfunction (increased genetic annotation and improved physiologic testing of CFTR). This article will place those advances in the context of CF diagnosis in the era of expanded CF therapeutics.

As part of the US CF Foundation Diagnosis Consensus Conference, convened in Phoenix, Arizona, in October 2015, the criteria for CF diagnosis were reviewed. This review included recent advances in changes to diagnosis for screened individuals, as well as for nonscreened. A summary of the conference was organized according to consensus statements and voted on by participants in the conference, as well as opened to public comment. The summary review and other articles can be viewed as part of this Supplement.[14-18] The consensus statements pertaining specifically to nonscreened individuals are listed in **Table I**.

Steps to Establish CF Diagnosis

When the diagnosis of CF is being considered outside of the NBS context, the presenting signs and symptoms (**Table II**) play an important role in defining likelihood of CF. An individual with multiple typical-organ system manifestations of CF (bronchiectasis, sinus polyps, and pancreatic insufficiency) has a higher probability of having CFTR dysfunction as the explanation of their phenotype compared with someone with only atypical manifestations of CF (eg, isolated symptoms such as chronic cough or sputum production without bronchiectasis, recurrent pancreatitis) that may have alternative explanations. Therefore, diagnosis of CF can be heavily influenced by the pretest probability or how well the phenotype is consistent with CF as we understand it now.

Coincident with the consideration of presenting signs and symptoms for CF, the clinician must also compare these with

Table II. Clinical signs/symptoms that may signify CF

Presenting conditions	Common as first presentation of CF	Uncommon as first presentation of CF*
Family history	Sibling or parent with CF	Parent of a child diagnosed with CF
Sinus	Chronic sinusitis, nasal polyps	
Lower respiratory	Bronchiectasis, chronic or recurrent lower airway infection (especially *Pseudomonas* infection)[22]	ABPA, nontuberculous mycobacterial infection, asthma, chronic obstructive pulmonary disease
GI/lumen	Meconium ileus, distal intestinal obstruction syndrome	Abnormal motility, rectal prolapse
GI/hepatobiliary	Pancreatic insufficiency, recurrent pancreatitis	Elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies (may present as ecchymosis, anemia, edema, night-blindness, skin rash)
Reproductive	Male infertility because of obstructive azoospermia (CBAVD)	Female infertility
Other	Hyponatremic dehydration,failure to thrive	Pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing

ABPA, allergic bronchopulmonary aspergillosis; *GI*, gastrointestinal.
*Many of the uncommon presentation clinical features are not uncommon in patients with CF (ABPA, nontuberculous mycobacterial infection, abnormal motility, clubbing, vitamin deficiencies), however, they are uncommon as isolated presenting complaint that ultimately is due to CF. Atypical mycobacterial infection has more commonly led to a diagnosis of CF in adults.[23,24]