Instructions:

BEFORE YOU START: Review the draft document *Lung Transplant Referral for Individuals with cystic fibrosis: Cystic Fibrosis Foundation Consensus Guidelines*

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

SECTION 2: General Feedback: Select your answer to the question, and then if directed, use the text box to provide additional information

SECTION 3: Recommendation Statement Feedback: Review the draft recommendation statements and associated supporting evidence and provide any comments

SECTION 4: Other Sections of the Manuscript Feedback: Use the text box to provide any additional comments on the other sections of the manuscript such as the introduction, methods, tables and figures, and international perspective

SECTION 5: Additional Feedback: Use the text box to provide any additional feedback that was not previously captured.

Lung Transplant Referral for Individuals with cystic fibrosis: Cystic Fibrosis Foundation Consensus Guidelines

Kathleen J. Ramos, Patrick J. Smith, Edward F. McKone, Joseph M. Pilewski, Amy Lucy, Sarah E. Hempstead, Erin Tallarico, Albert Faro, Daniel B. Rosenbluth, Alice L. Gray, and Jordan M. Dunitz for the CF Lung Transplant Referral Guidelines Committee

1. Introduction

Many individuals with cystic fibrosis (CF) die from respiratory failure without referral for lung transplantation (LTx)[1, 2]. LTx evaluation is best initiated for individuals with advanced but not end-stage lung disease; emergent inpatient referral does not allow time for careful consideration of the LTx option and is not universally available. Early referral for LTx gives individuals with CF the opportunity to learn more about the risks and benefits of LTx, both generally and specific to their clinical situation, so they can make informed decisions. Early referral for LTx evaluation increases the likelihood of an individual being a candidate for transplant by giving the patient an understanding of their specific barriers to LTx, as well as an opportunity to address those barriers. While some individuals who meet criteria for referral will be "too early" for listing, it is important to recognize that referral does not necessarily lead to a full evaluation or listing, but instead gives individuals with CF, their families, and providers access to the expertise of the LTx team. Progressing from routine CF care to LTx can be viewed as a transition. Just like the transition from pediatric to adult care, it is facilitated by education, communication and support for the individual and family. Timely referral for LTx allows individuals to be medically, psychosocially, and financially prepared for LTx should the need arise. While there may be not be a perfect “window” for referral, prioritizing inclusive policies reduces the likelihood that eligible patients miss an opportunity for LTx. The goal of these Consensus Guidelines is to provide pragmatic recommendations and guidance to the CF community to allow for better identification and timely referral of those individuals with CF who have advanced lung disease (ALD).

2. Methods

The CF Foundation invited a multidisciplinary team including adult and pediatric CF and transplant pulmonologists, a clinical psychologist, a social worker, a transplant recipient with CF, a former CF nurse, and a transplant coordinator to participate in development of consensus guidelines. The committee met for a virtual kickoff meeting on September 26, 2017 to determine the scope of the work and divide into three workgroups focusing on: understanding the timing for transplant referral; an emphasis on early referral and modifiable barriers; and transition to transplant. Several PICO (Population, Intervention, Control, Outcome) questions were developed. The workgroups performed individual literature searches in PubMed. Information about the specific literature searches can be found in Supplement X.

The workgroups developed draft recommendations based on the results of the search. Workgroups discussed the recommendations on monthly phone calls. The committee reconvened on May 11, 2018 to revise and adopt the draft recommendation statements. An a priori voting threshold of 80% agreement was established. On September 19, 2018, the guidelines were distributed for public comment.

Focus Group

As part of the consensus guidelines, a focus group of seven CF transplant recipients and two spouses of recipients (hereafter referred to as "the focus group") was organized. Although focus group content and data synthesis are qualitative by nature, these ancillary data sources can provide informative clinical data [3, 4]. The focus group participated in seven, one-hour long video-calls led by a transplant psychologist (PJS) and an adult with CF (AL). Following an introductory session during which thematic content was identified and analyzed, the focus group participated on five content-specific calls and one summary review call. Themes identified during the introductory call included: 1) timing of transplant information presentation, 2) transplant-related expectations, 3) treatment team transition issues, 4) stigma associated with the need for transplantation, and 5) concerns regarding social support during the transition to transplant. All calls were video- and audio-recorded in order to facilitate re-analysis by focus group leaders.

3. Discussion of Recommendation statements listed in Table 1

1. The CF Foundation recommends clinician-led efforts to normalize lung transplant as a component of clinical care through discussions regarding disease trajectory and treatment options including lung transplantation during annual clinic visits

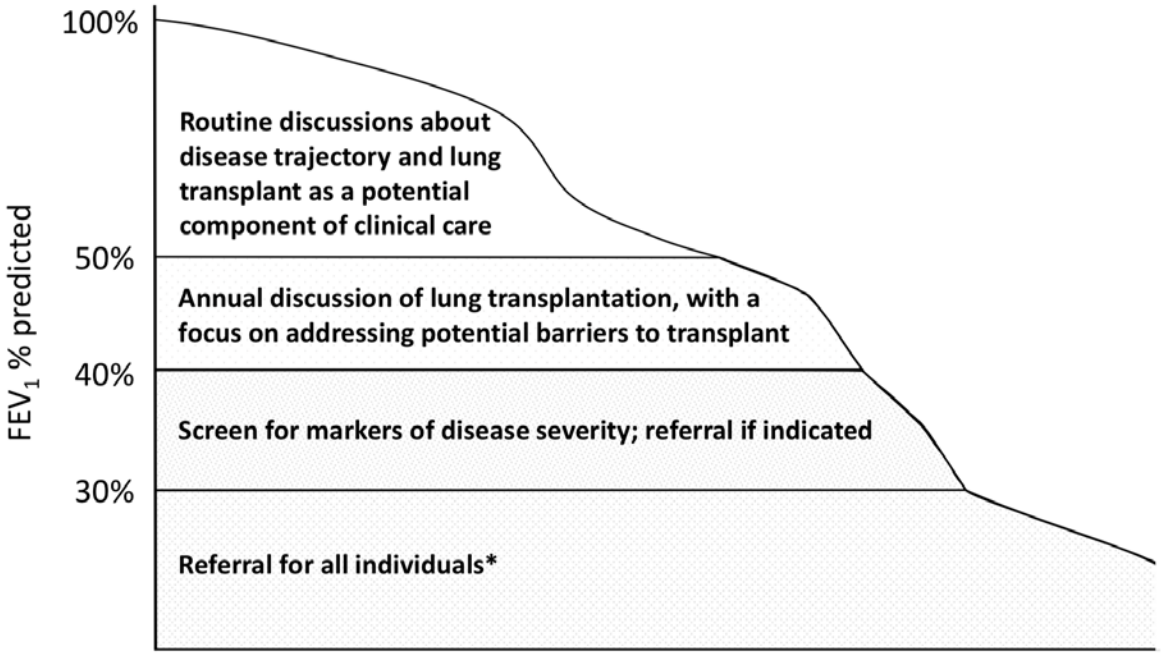
For individuals with CF, post-transplant survival is increasing, with the current ISHLT report documenting 9.2 years median survival among adults with CF[5]; therefore, periodic discussion of LTx is recommended to help destigmatize the procedure. Numerous members of the focus group noted that early introduction and normalization of LTx facilitated a more effective transition/referral process. In contrast, when LTx was introduced in the context of clinical deterioration, it was associated with increased fear, denial, and potential delay and/or avoidance of important clinical elements of care. Many focus group members, characterized their impressions of LTx as 'a death sentence', 'the beginning of the end', or with similarly negative connotations, despite the improving post-transplant survival outcomes (Table 2). It was also noted in the focus group that individuals' feelings toward transplant strongly mirrored that of their physician(s). For example, a strong association was noted between physicians who reportedly exhibited a negative bias towards transplant and individuals who felt fear, anxiety, and a sense of personal failure. In contrast, individuals whose physicians reportedly regarded transplant more positively, and who approached transplant as a viable treatment option for end-stage CF, felt more informed, confident, and optimistic about their future quality of life. Several specific recommendations in the consensus guidelines may help accomplish the broader goal to normalize discussion of LTx, including earlier physician-patient discussions of LTx as a viable treatment option for end-stage CF, the use of up-to-date, understandable sources of information related to LTx [6, 7], and alternative discussion points for clinicians (Table 2).

2. The CF Foundation recommends CF care team initiated discussion regarding lung transplantation with all individuals with CF and an FEV_1 less than 50% predicted

While many studies have demonstrated an association between forced expiratory volume in one second (FEV_1) and mortality[8-14], FEV_1 is an imperfect marker of disease severity. Survival with low lung function is improving, and some individuals with CF live for prolonged periods with severely reduced lung function while others die quickly following a decline in FEV_1 [1, 8, 15]. Determining which FEV_1 (best, worst, "baseline", or during an exacerbation) should prompt action is challenging. Expert

consensus concluded that an FEV_1 <50% predicted, regardless of the context, should prompt discussion of LTx as a potential therapeutic option (Figure 1). This discussion serves as an opportunity to identify barriers to LTx and to clarify the individual's goals of care (See Table 3). Some potential barriers to LTx could require years of work to correct in order for an individual to become an acceptable candidate. Early discussion may permit this opportunity.

Figure 1: Lung function thresholds for communication about lung transplantation and timing of lung transplant referral



*In the presence of contraindications, recommend discussion with at least two transplant centers prior to determining that an individual is not a transplant candidate

3. The CF Foundation recommends that the individual's CF care team elicit and address CF-specific psychosocial and physical concerns about lung transplantation to facilitate transition to transplant

Numerous psychosocial, physical, and care-related concerns emerged from the focus group as being particularly salient among individuals with CF. Increased complexity of care, the potential for de-centralization of care (leaving the CF center), worsening impairments in quality of life at a young age, the potential loss of CF identity, concerns regarding family planning, relationship issues, and education/career could influence their approach to the transplant process. There is decreased access to referral, listing and LTx for individuals with CF and lower socioeconomic status (e.g. Medicaid insurance status)[16, 17]. Geographic disparities in access to LTx are an important consideration for people with CF [16]. Although Hispanic individuals with CF tended to have milder phenotypes, a recent study demonstrated increased risk of death without LTx and a younger age at death for Hispanic individuals

with CF[18]. Providing support to individuals with CF during the transition requires an understanding of these (and other) CF-specific psychosocial concerns.

4. The CF Foundation recommends the use of up-to-date CF-specific transplant resources to promote understanding of the transplant journey and to minimize misconceptions regarding outcomes

Individuals with CF and their families should have access to contemporary, CF-specific information regarding LTx in order to optimize their understanding of potential transplant outcomes. These data can be found on the websites of several organizations, including the Cystic Fibrosis Foundation (CFF.org), the International Society for Heart and Lung Transplantation (ISHLT) (ishlt.org), and the Scientific Registry of Transplant Recipients (SRTR.org). Decision aids or other technology-based sources of information could be useful to highlight misconceptions/misunderstanding and facilitate an accurate fund of knowledge regarding LTx. Another potential resource is connecting people with CF with each other to address concerns regarding LTx[7].

5. The CF Foundation recommends the CF and lung transplant care teams acknowledge and provide support for mental health concerns regarding the referral and evaluation process for transplant that are unique to individuals with CF

Many focus group members noted that the idea of requiring LTx may elicit reflexive, internal attributions that the need for transplant reflects a failure of their own adherence behaviors. Because the importance of adherence-related behaviors is often underscored for many individuals with CF, and these behaviors are integrally tied to clinical functioning in younger individuals with CF, this implicit association may inadvertently elicit feelings of shame[19, 20] or stigma[21]. For example, many individuals in the focus group characterized coping styles that would 'fight' or 'beat' CF through vigilant adherence behaviors[22-24]. Providers are encouraged to identify and address individuals' negative self-directed emotions because they can lead to avoidance of clinical interactions and delay the receipt of appropriate care[25, 26]. In addition, providers should be aware that the introduction of uncertainty about patients' *eligibility* for LTx may serve to increase ambivalence and ultimately avoidance of transplant-related knowledge or health decisions [27, 28]. Moreover, depression and anxiety are common among individuals with CF[29] and may adversely impact LTx outcomes[30].

6. For individuals with CF 18 years of age and older, the CF Foundation recommends lung transplant referral no later than when:

- FEV_1 is <50% predicted and rapidly declining (>20% relative decline in FEV_1 within 12 months)

OR

- FEV_1 is <40% predicted with markers of shortened survival (including, those noted in recommendation #10, 14, 15, 16, and 18)

OR

- FEV_1 is <30% predicted

Because FEV_1 is associated with mortality[8-14], FEV_1 thresholds were identified to prompt further action, including evaluation for markers of shortened survival (discussed below) and/or lung transplant referral. Markers of shortened survival include low FEV_1, 6-minute walk test (6MWT) distance <400 meters, hypoxemia (SpO_2 <88% or P_aO_2 <55 mmHg, at rest or with exertion), hypercarbia (P_aCO_2 >50 mmHg, confirmed on arterial blood gas), pulmonary hypertension (PA systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet), BMI <18 kg/m^2, increased frequency of pulmonary exacerbations (>2 exacerbations per year requiring IV antibiotics or one exacerbation requiring positive pressure ventilation), massive hemoptysis, or pneumothorax.

Although FEV_1 alone should not determine timing of lung transplant referral, referral should occur no later than when the non-exacerbation ("stable") FEV_1 is <30% predicted. Among individuals with a "stable" FEV_1 <30% predicted in the US, approximately 10% die without LTx each year after reaching this threshold[1]. For individuals with frequent exacerbations, it may be difficult to assess a "stable" FEV_1, but these individuals may benefit from referral (see recommendation #15). Rapidly declining FEV_1 has been shown to predict death without LTx[15, 31, 32]. A recent study of a sample of individuals with CF who died in the US found that 38% had a documented "highest" FEV_1 that was greater than 40% in the year prior to death, highlighting that a rapid decline in FEV_1 may precede death for many individuals with CF[33]. Recommendations 10, 14-16, and 18 identify individuals with risk profiles highlighted in published prognostic models[8, 10-14].

7. For individuals with CF under the age of 18 years, the CF Foundation recommends lung transplant referral when the FEV_1 is <40% predicted

Individuals with CF frequently transition to adulthood with FEV_1 in the normal or only mildly impaired range, with only 5% of 18 year olds having severe lung disease (FEV_1 <40%) in 2015[34]. Children with CF tend to do worse than adults with the same FEV_1 % predicted. For this reason, expert consensus was that children with CF under age 18 years should be referred for LTx at an earlier FEV_1 threshold than the average adult individual [31]. For children with markers of increased disease severity (including those noted in recommendation 10, 14-16, and 18) consideration for referral prior to the FEV_1 <40% threshold is recommended.

8. For individuals with CF and an FEV_1 <40% predicted, the CF Foundation recommends an annual 6-minute walk test (6MWT), assessment of need for supplemental oxygen and venous blood gas to screen for markers of severe disease that may warrant transplant referral

The 6-minute walk test (6MWT) distance is used regularly in Canada, Ireland and other parts of the world to assess the clinical status of individuals with advanced/deteriorating CF lung disease[35, 36]. Expert consensus was that annual testing with a 6MWT, an assessment for supplemental oxygen requirement, and venous blood gas (VBG) would provide clinically meaningful data for patients with ALD. Assessment for supplemental oxygen requirement (SpO_2 <88% or P_aO_2 <55 mmHg) should occur at rest, with exertion, and during sleep [8, 37-39]. An annual VBG should be used to screen for hypercarbia,

and if P_vCO_2 is elevated (P_vCO_2 >56 mmHg), a confirmatory arterial blood gas (ABG) should be obtained. In the pediatric population, consider performing testing prior to reaching the FEV_1 <40% threshold.

9. For individuals with CF 18 years of age and older with FEV_1 <40% predicted, the CF Foundation recommends a baseline echocardiogram to screen for pulmonary hypertension

Pulmonary hypertension is common in individuals with advanced CF-related lung disease[39-43], but its presence is rarely identified prior to evaluation for LTx. Repeat echocardiogram should be considered for individuals with worsening clinical status.

10. The CF Foundation recommends lung transplant referral, regardless of FEV_1, when there are markers of shortened survival, including:

- 6MWT distance <400 meters

OR

- hypoxemia (at rest or with exertion)

OR

- hypercarbia (P_aCO_2 >50 mmHg, confirmed on arterial blood gas)

OR

- pulmonary hypertension (PA systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet)

Individuals with FEV_1 greater than 40% predicted are unlikely to have these data available unless their clinical status is out of proportion to their FEV_1.

The 6MWT distance is associated with death or LTx for individuals with CF[42, 44-46]. The ISHLT recommends referral for LTx evaluation when the 6MWT distance is less than 400 meters[47]. Although a sub-maximal exercise test for a majority of individuals with CF, the 6MWT is a marker of functional status and may better reflect limitations experienced by individuals with ALD than the FEV_1 alone.

Supplemental oxygen requirement and/or low P_aO_2 have been repeatedly associated with death without LTx for individuals with CF[1, 8, 37, 42, 48, 49]. Arterial hypercarbia is a known predictor of death in individuals with CF [8, 12, 39, 50]. Pulmonary hypertension has been associated with death without lung transplant [51-53], but echocardiograms are imperfect at determining the severity of pulmonary hypertension in patients with ALD and may identify “false positive” cases[54, 55] . In an individual with FEV_1 <40% whose only marker of increased disease severity is an elevated PA systolic pressure (>50 mmHg), a confirmatory right heart catheterization may be warranted prior to transplant referral.

11. The CF Foundation recommends that modifiable barriers to lung transplantation be addressed preemptively to optimize transplant candidacy; however, unresolved barriers should not preclude

referral. Potentially modifiable barriers may include but are not limited to: sputum microbiology, nutritional status, diabetes management, renal insufficiency, liver disease, adherence behaviors, mental health issues, substance use, and psychosocial factors

The number of individuals with CF who die each year without lung transplant referral remains significant[1]. A survey of physicians in the US demonstrated that potentially modifiable barriers are a frequent reason for non-referral[56]. Modifiable barriers to transplant should be identified preemptively in CF clinic, potentially years prior to the need for LTx; these do not need to be fully resolved prior to a referral (Table 3). Transplant providers may help those individuals with modifiable barriers better understand how these issues negatively impact their transplant candidacy and provide tools and motivation to mitigate these barriers. The transplant program can assess potentially modifiable barriers in the context of transplant candidacy as a whole, to determine exactly what progress needs to be made in order for someone to become an acceptable candidate for transplant. Additionally, non-medical barriers to LTx, including insurance status, geography, finances, medical literacy, and limited social support, may influence not only when to refer for transplant, but also where to refer. Certain psychosocial factors may take years to optimize prior to a lung transplant referral.

12. The CF Foundation recommends CF clinician consultation with local and geographically distant lung transplant centers for individuals with microorganisms that may pose a risk for lung transplantation (e.g. Burkholderia cepacia complex, nontuberculous mycobacterium)

Infection with certain microorganisms (e.g. Burkholderia cepacia complex, nontuberculous mycobacterium, multi-drug resistant microorganisms) is associated with worse outcomes following lung transplantation[14, 47, 57-62]. These microorganisms may be considered absolute contraindications at some transplant programs and acceptable at other institutions. Similarly, infection with a particular organism may not in and of itself be considered an absolute contraindication by a program, but if combined with other risk factors, may be a reason an individual is declined for LTx.

13. The CF Foundation recommends consultation with at least two transplant centers before determining that an individual is not a transplant candidate

Each lung transplant program has its own criteria for transplant candidacy and listing. Criteria differ widely based on institutional experience, resources and risk thresholds. Center practices may also evolve over time. Individuals who are declined at one transplant center may be deemed suitable at another center.

14. The CF Foundation recommends lung transplant referral in adults with CF with a BMI <18 and FEV_1 <40% predicted while concurrently working to improve nutritional status

Studies have shown low BMI is a risk factor for death without lung transplantation[1, 10, 11, 14, 63, 64] and it should be considered a marker of urgency for lung transplant referral. Minimum BMI thresholds vary from center to center and low BMI should be proactively addressed (enteral tube feeding guidelines)[65] as a modifiable barrier to transplant. While a specific BMI cutoff is not useful for defining

malnutrition in the pediatric population and a weight-for-age >10th percentile is a common goal[66], malnutrition is an important modifiable barrier to lung transplantation for children with CF [67] and should be addressed concurrently with referral for children with ALD.

15. The CF Foundation recommends lung transplant referral of individuals with FEV_1 <40% predicted and >2 exacerbations per year requiring IV antibiotics or 1 exacerbation requiring positive pressure ventilation regardless of FEV_1

Increasing number of pulmonary exacerbations is associated with death without transplant among individuals with ALD, with risk increased in the setting of 1 or more courses of IV antibiotics[1, 9, 13, 14, 68] or the need for hospitalization[10, 11, 13, 14, 37]. The presence of acute hypercapnic or hypoxemic respiratory failure, or chronic hypercapnic respiratory failure, necessitating positive pressure ventilation (e.g. noninvasive or invasive ventilatory support), in the hospital or home setting, should prompt referral for LTx regardless of FEV_1.

16. The CF Foundation recommends referral for lung transplant evaluation of individuals with FEV_1 <40% predicted and massive hemoptysis (>240mL) requiring ICU admission or bronchial artery embolization

Hemoptysis increases the risk for death or LTx [69, 70]. There may be an increased risk for hypercapnic respiratory failure and death following bronchial artery embolization among individuals with ALD[71]. It is expert consensus that among individuals with CF and FEV_1 between 30% and 40% predicted, an episode of hemoptysis leading to ICU admission and/or bronchial artery embolization should prompt referral for LTx evaluation. Individuals referred for hemoptysis may have risk that is not captured in the lung allocation score (LAS), and serious hemoptysis may occur without warning, potentially prompting lung transplant centers to request an exception to the LAS. Additionally, individuals with CF and FEV_1 >40% may also warrant LTx evaluation if episodes of hemoptysis are frequent and severe.

17. For women with CF, especially those who are younger or short stature, the CF Foundation recommends special consideration for lung transplant referral even when other thresholds have not been met

There is a persistent gender gap in survival for individuals with CF[1, 8-11, 49, 72, 73] and this recommendation aims to focus providers on the increased risk of death for women with CF. Special consideration for LTx referral is recommended for women who are younger (age 18-25 years), have shorter stature (under 162 cm)[74], CF-related diabetes, rapidly declining FEV_1, or rapidly declining BMI.

18. The CF Foundation recommends consideration of early lung transplant referral for individuals with FEV_1 <40% predicted and pneumothorax

The occurrence of pneumothorax is more frequent among individuals with CF and severe pulmonary impairment (FEV_1 <40%) and older age, leading to an increased number of hospitalizations and number of days spent in the hospital, and an increase in 2-year mortality for individuals with this

complication[75]. Recurrent pneumothorax is an indication for referral for LTx in the ISHLT recommendations for individuals with CF[47]. This complication is a marker of increased disease severity, is associated with decreased survival, and may impact surgical planning for LTx.

19. The CF Foundation recommends that CF clinicians develop relationships with peers at partnering transplant centers to:

- optimize the transition to transplant, starting with referral
- understand transplant center-specific practices, including navigating complex socioeconomic barriers to transplant
- maintain ongoing dialogue about clinical status of individuals listed or approaching transplant listing

Identifying peers at partnering transplant centers allows for improved communication and facilitates continuity of care. CF care teams can deliver the best care to individuals at their home CF Center when they are aware of the partnering lung transplant center practices. Clear communication of the necessary medical information at the time of transplant referral will streamline the process and increase efficiency for both teams. Maintaining a relationship between the CF team and partnering transplant team is key to facilitate a smooth transplant referral and ongoing co-management of individuals in the pre-transplant phase. CF providers, including all members of the CF care team, can reinforce the importance of ongoing work by the individuals with CF and caregivers to address outstanding concerns.

20. The CF Foundation recommends communication between the CF and lung transplant care teams every 6 months and with major clinical changes to discuss individuals referred but not listed for transplant to review clinical status and progress addressing transplant team recommendations

Timely referral for LTx allows individuals with CF to establish a relationship with the transplant team, obtain transplant specific education, and identify and modify barriers to transplant. For individuals with CF deemed “too early” for listing, ongoing discussion at set time intervals will allow for continued assessment of disease progression (e.g. development of markers of increased disease severity noted in recommendation 10, 14-16, and 18; significant clinical events) and readiness for transplant. For individuals deferred due to barriers, dialogue should highlight progress toward addressing barriers to transplant. Further, because certain characteristics such as height, chest cavity size, ABO blood type and HLA sensitization may result in challenges finding a suitable donor, it is critical for the transplant team to be aware of changes in clinical status, which may affect transplant candidacy as well as timing for listing. Open lines of communication between the CF and lung transplant care teams regarding patients who are listed or approaching listing are vital if an individual has a sudden deterioration. Geographic and program-specific donor availability and waitlist times may influence the timing of listing. Finally, local lung transplant center practices will necessarily influence how CF providers interpret and implement these consensus recommendations.

21. The CF Foundation recommends research on factors contributing to lack of transplant referral for individuals with CF and FEV_1 <30% predicted or those with higher lung function who die of respiratory disease

Evidence indicates that many individuals with CF who die from respiratory disease are never referred for transplant[2, 17]. Presumably, some deaths may have been prevented if LTx had been considered and a referral made. Available data suggests the reasons for non-referral may not be due to absolute contraindications to transplant[2]. More research is needed to understand why some individuals with ALD are not referred and which individuals are at greatest risk of dying without transplant referral.

4. International perspective

Outside of the U.S., there is a broadly similar experience with delays in referral for lung transplant. Both European and Australian CF patient registries show that many individuals die without receiving LTx. It is not known, however, whether these individuals were in the process of assessment or had been considered for transplant prior to death. It is likely that similar barriers to LTx seen in the U.S. exist in many countries and guidelines for timely referral for lung transplant assessment are welcome. In addition to the barriers outlined earlier in this statement, there are a number of unique challenges in Europe as many of the smaller European countries do not have a transplant program and must refer to neighboring countries. This leads to further barriers such as inability of very sick individuals to travel (often significant distances by air), language and cultural difficulties throughout the transplant process, and complexities of cross-country funding and follow-up. Even in countries with well-established programs, many individuals with CF die without receiving LTx [2]. In the UK, in a recent survey of 28 specialty CF centers[76] 22% of respondents expressed concerns that LTx was discussed with patients too late and 19% expressed concerns that individuals with CF were referred for transplant assessment too late. Barriers to referral in the UK included patient refusal, poor-adherence and psychological readiness as well as unexpected rapid clinical deterioration or the presence of significant comorbidities/infections that could preclude transplant. In France, with a well-developed National Lung Transplant Program, including the introduction of an emergency transplant program in 2007, 50% of all CF deaths occur without lung transplantation of which 72% had at least one indication for transplant and were not on the active transplant list [2]. Although the majority of these individuals were in the process of lung transplant assessment or had been declined for LTx, 39% of these potentially eligible individuals with CF had never been considered for transplant[2]. A subsequent survey of French centers[77] proposed an earlier structured approach to transplant assessment including improved patient and caregiver education and earlier discussions of transplant options. These studies, in countries with well-established transplant programs and specialized CF centers, highlight that transplant referral challenges are worldwide and that barriers to early referral need to be identified and overcome.

5. Conclusions and next steps

Survival for individuals with CF has improved dramatically over the past few decades and this improvement may accelerate with new agents that address the cellular defect in CF. Nevertheless, the majority of individuals with CF still eventually succumb to their lung disease. LTx has the potential to extend survival. Despite this fact, many individuals with CF die without ever being considered for

transplantation. These guidelines are intended to help CF providers appropriately counsel their patients about LTx. The journey through referral, evaluation, listing and transplantation is fraught with physical and psychosocial challenges for the individual and their family. It is the responsibility of both the CF team and the transplant team to provide support through this transition. Many of the barriers to LTx can be overcome if identified and addressed early enough in the course of the disease to permit adequate time for resolution. While data is limited, there is a growing body of literature to support the use of FEV_1 combined with other physiologic parameters including pulmonary artery pressure, hypoxia, hypercarbia, trajectory of lung function and nutritional status to determine appropriate timing of referral.

Table 1: Recommendation Statements

	Recommendation	% Consensus
1	The CF Foundation recommends clinician-led efforts to normalize lung transplant as a component of clinical care through discussions regarding disease trajectory and treatment options including lung transplantation during annual visits in clinic	100%
2	The CF Foundation recommends CF care team initiated discussion regarding lung transplantation with all individuals with CF and an FEV_1 less than 50% predicted	100%
3	The CF Foundation recommends that the individual's CF care team elicit and address CF-specific psychosocial and physical concerns about lung transplantation to facilitate transition to transplant	100%
4	The CF Foundation recommends the use of up-to-date CF-specific transplant resources to promote understanding of the transplant journey and to minimize misconceptions regarding outcomes	100%
5	The CF Foundation recommends the CF and lung transplant care teams acknowledge and provide support for mental health concerns regarding the referral and evaluation process for transplant that are unique to individuals with CF	100%
6	For individuals with CF 18 years of age and older, the CF Foundation recommends lung transplant referral no later than when: • FEV_1 is <50% predicted and rapidly declining (>20% relative decline in FEV_1 within 12 months) OR • FEV_1 is <40% predicted with markers of shortened survival (including, those noted in recommendation #10, 14, 15, 16, and 18) OR • FEV_1 is <30% predicted	100%
7	For individuals with CF under the age of 18 years, the CF Foundation recommends lung transplant referral when the FEV_1 is <40% predicted	100%
8	For individuals with CF and a FEV_1 <40% predicted, the CF Foundation recommends an annual 6-minute walk test (6MWT), assessment of need for supplemental oxygen and venous blood gas to screen for markers of severe disease that may warrant transplant referral	100%
9	For individuals with CF 18 years of age and older with FEV_1 <40% predicted, the CF Foundation recommends a baseline echocardiogram to screen for pulmonary hypertension	100%

10	• The CF Foundation recommends lung transplant referral, regardless of FEV_1, when there are markers of shortened survival, including: • 6MWT distance <400 meters OR • hypoxemia (at rest or with exertion), OR • hypercarbia ($PaCO_2$ >50 mmHg, confirmed on arterial blood gas), OR • pulmonary hypertension (PA systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet)	100%
11	The CF Foundation recommends that modifiable barriers to lung transplantation be addressed preemptively to optimize transplant candidacy; however, unresolved barriers should not preclude referral. Potentially modifiable barriers may include but are not limited to: sputum microbiology, nutritional status, diabetes management, renal insufficiency, liver disease, adherence behaviors, mental health issues, substance use, and psychosocial factors	100%
12	The CF Foundation recommends CF clinician consultation with local and geographically distant lung transplant centers for individuals with microorganisms that may pose a risk for lung transplantation (e.g. Burkholderia cepacia complex, nontuberculous mycobacterium)	100%
13	The CF Foundation recommends consultation with at least two transplant centers before determining that an individual is not a transplant candidate	100%
14	The CF Foundation recommends lung transplant referral in adults with CF, with a BMI <18, and FEV_1 <40% predicted, while concurrently working to improve nutritional status	100%
15	The CF Foundation recommends lung transplant referral of individuals with FEV_1 <40% predicted and >2 exacerbations per year requiring IV antibiotics or 1 exacerbation requiring positive pressure ventilation regardless of FEV_1	100%
16	The CF Foundation recommends referral for lung transplant evaluation of individuals with FEV_1 <40% predicted and massive hemoptysis (>240mL) requiring ICU admission or bronchial artery embolization	100%
17	For women with CF, especially those who are younger or short stature, the CF Foundation recommends special consideration for lung transplant referral even when other thresholds have not been met	100%
18	The CF Foundation recommends consideration of early lung transplant referral for individuals with FEV_1 <40% predicted and pneumothorax	100%

19	The CF Foundation recommends that CF clinicians develop relationships with peers at partnering transplant centers to: • optimize the transition to transplant, starting with referral • understand transplant center-specific practices, including navigating complex socioeconomic barriers to transplant • maintain ongoing dialogue about clinical status of individuals listed or approaching transplant listing	100%
20	The CF Foundation recommends communication between the CF and lung transplant care teams every 6 months and with major clinical changes to discuss individuals referred but not listed for transplant to review clinical status and progress addressing transplant team recommendations	100%
21	The CF Foundation recommends research on factors contributing to lack of transplant referral for individuals with CF and FEV_1 <30% predicted or those with higher lung function who die of respiratory disease	100%

396

397

398 Table 2: Focus group-derived themes and considerations for communication with individuals with cystic
399 fibrosis

Thematic Domain	Provider Exemplars from Focus Group	Effective Alternative Exemplars for Clinicians
Normalizing the need for lung transplantation	- 'We will think about transplant when it's time [for transplant]' - 'Transplant is to be avoided if at all possible.' - 'You're trading one disease for another.'	- 'Transplant is often considered as a next step as CF worsens.' - 'Many -individuals with CF will undergo transplant as a component of their care when other therapies no longer work.' - 'What have other providers told you, if anything, about the risks and benefits of transplant?' - 'Tell me what your understanding of transplant is so that I can help provide more information.' - 'While there are certainly risks associated with transplantation, there is a very good chance that it will increase the quality and length of your life.'
Eliciting and addressing CF-related concerns and outcomes	-'Your lungs have failed you.' -'We [treatment team] have failed you.' -'You fought hard but lost the battle.' -'Your test results indicate we need to move forward with a transplant referral. We will set up your appointments.'	- 'You've fought hard and done your part. For most people living with CF, lung function will eventually worsen to the point where we consider transplant, no matter how hard you fight.' - 'We did the best we could and now need to consider transplant as the next step to best treat your CF.'

		- 'Most people have some concerns about transplantation. Help me to understand yours.' - 'Your test results suggest that we may need to consider a transplant evaluation. What thoughts do you have, if any, about that possibility?'
Addressing transplant-related expectations	- 'Recipients only live 5 years.' - 'Many patients don't do well after transplant.' - 'Transplant is a death sentence.'	- 'Everyone's transplant experience is different and unique. For people with CF the median post-transplant survival is almost 9 years. That means that half of the people who undergo lung transplantation for CF live for more than 9 years, many significantly more. - 'Individuals with CF who receive lung transplants show the greatest health and quality of life benefits compared to other lung transplant recipients. Although there are potential complications, the vast majority are manageable. '

400

401

402

403 Table 3: Clinical and educational milestones for lung transplant referral

At diagnosis of CF and throughout the life-span	- Individuals with CF should establish and maintain care with a physician trained in the natural history, prognosis, and treatment options for CF - Discuss lung transplantation early in the course of disease as a means to normalize this component of clinical care. Introduce it as a potential treatment option that prolongs life for individuals with CF - Frame lung transplantation in a positive manner, instead of as a "last resort" or "failure of therapy," because care team attitudes affect willingness to discuss lung transplantation when it becomes medically necessary for individuals with CF - Utilize up-to-date, CF specific, resources when providing lung transplant outcomes information
When lung function declines to FEV_1 <50% predicted	- Discuss values and goals of care - Implement all indicated medical therapies to optimize lung function and overall health - Discuss ways to optimize health/lung function to delay lung transplantation, and the importance of adherence pre- and post-transplant - Optimize BMI with appropriate nutrition interventions - Initiate discussion regarding lung transplantation; early discussion gives individuals with CF time to consider lung transplantation when it is not urgently needed - Note that lung transplant referral is not an event, it is a process that begins with informed discussions of benefits, risks, indications, and contraindications - Elicit and address CF-related concerns about lung transplantation, such as: fear, shame, and giving up the "fight" against CF - Explain the logistics of lung transplantation at the "home" CF Center - Assess for potential barriers to transplant: medical, psychosocial, financial - Discuss potential geographic barriers to lung transplant (e.g. potential need to relocate, distance to travel for evaluation, insurance limitations to lung transplant center options for coverage) - Acknowledge differences in clinical outcomes and the potential need for increased support for individuals with disadvantaged backgrounds
When lung function declines to FEV_1 <40% predicted	- Increase frequency of CF clinic visits, if indicated, to address contributing factors - Emphasize the importance of nutrition, diabetes control, physical conditioning, self-care, mental health, adherence, and social support and correlate them with clinical outcomes and implications for candidacy for transplant

	- Evaluate for markers of shortened survival using 6-minute walk test, oxygen desaturation study, nocturnal oximetry, blood gas, echocardiogram - Assess for organisms with implications on transplant candidacy (such as: NTM, fungus, and Burkholderia species) - **Referral for individuals with markers of increased severity of disease** (e.g. 6-minute walk test distance <400 meters, supplemental oxygen requirement, arterial hypercarbia, pulmonary hypertension). Discuss implications for decreased survival in the presence of markers of increased severity of disease as the rationale for referral to consider lung transplantation - **Referral for all individuals under 18 years of age**
When lung function declines to FEV_1 <30% predicted	- **Referral for all individuals** - Continue at least annual monitoring for markers of shortened survival. Individuals with CF can have prolonged survival with FEV_1 <30% predicted, but it is important to continue monitoring for complications of CF that increase the risk of death without lung transplant - Update the local transplant center every 6 months or with clinical changes
Modifiable barriers to lung transplantation	- Malnutrition (BMI less than 17 kg/m^2) may be a contraindication to lung transplantation, but is modifiable. As lung disease progresses, malnutrition becomes more prevalent. Recommend use of enteral tube feed guidelines for management of malnutrition - CF-related diabetes can be associated with increased pulmonary exacerbations, weight loss, and lung function decline. Suboptimal management of diabetes may be a marker of non-adherence and treatment could slow disease progression. Diabetes control should be optimized to maximize medical management of advanced CF and minimize transplant-associated risk - Chronic narcotic use may impair post-lung transplant pain management and may be a contraindication at certain centers - Substance use has been associated with worse post-transplant outcomes and there are center-specific rules related to substance use - Promote strategies to optimize adherence, as many transplant centers consider non-adherence a relative (and sometimes absolute) contraindication to listing/transplant - Early referral permits education and contract setting, if needed, and an opportunity to assess for capacity for adherence - Anxiety and depression are prevalent in individuals with CF, and become more prevalent with advanced lung disease and can impair recovery from transplant. Identify and treat mental health issues that may negatively impact transplant candidacy and outcomes

	- Address psychosocial barriers such as: caregiver support, finances, and health literacy
Special considerations	– Geographic and program-specific donor availability may influence the timing of listing and choice of transplant center – Insurance coverage may limit access to specific transplant centers – Complexity of surgical procedure may influence the choice of transplant center – Center-specific practices are dynamic and may change over time *The following may impact lung transplantation candidacy depending on transplant center-specific practices:* - Certain infections (*Burkholderia cenocepacia, Burkholderia gladioli, Burkholderia dolosa, Mycobacterium abscessus, Scedosporium prolificans*) - Renal insufficiency - Liver disease - Critical or unstable clinical condition (e.g. mechanical ventilation or ECMO) - Cardiac dysfunction - Prior thoracic surgery - Prior lung transplantation - History of cancer
Decision to initiate lung transplant referral	- It is important not to rely solely on the FEV_1 for timing of referral. Incorporate other markers of shortened survival into the referral decision: hypoxemia, hypercarbia, shortened 6-minute walk test distance, increasing frequency/severity of exacerbations, low BMI, pulmonary hypertension, massive hemoptysis, pneumothorax, female sex, and short stature - Refer early to avoid missing the lung transplant window - Refer early to give opportunity to explore other options if first transplant center declines the individual as a candidate - Provide detailed information about clinical history, markers of disease severity, and potential contraindications. - The balance of independence versus the need for social support is especially complex for adolescents and young adults - Acknowledge the stress, expense, invasiveness of procedures (e.g. colonoscopy, right heart catheterization), and waiting involved with referral and evaluation - Discuss insurance and financial implications - Assess geographic barriers to transplantation and identify transplant center where individual has the most social support - When a referral is “early,” it is an opportunity to get detailed information about transplant and serves as a second opinion that could identify important modifiable barriers to eventual transplantation

	- Referral during a crisis, or rapid decline, may limit an individual's access to transplant depending on local transplant center practices
Decision to defer listing	- Consult at least two lung transplant centers prior to determining that an individual is not a transplant candidate if the first center declines to list the individual because of a contraindication - If an individual is "too early" for listing, then establish a plan for continued monitoring and communication with the transplant team - Continued communication with the transplant center includes information about changes in clinical status, social situation, and goals of care
Decision to list for transplant	- Communicate with the transplant center about changes in the individual's status while listed - Lung Allocation Score (LAS) is used for determining lung transplant recipient priority in the US. Important components of the LAS include: age, FVC, pCO_2, oxygen requirement, BMI, 6MWT distance, pulmonary arterial pressure, presence of diabetes, diagnosis, and functional status - Continue to acknowledge the stress, expense, waiting time, and uncertainty for individuals awaiting lung transplant

404

405

<u>The CF Lung Transplant Referral Guideline Committee</u>:

Kathleen J. Ramos - Chair

Jordan M. Dunitz -Chair

Daniel B. Rosenbluth

Daniel J. Dorgan

Alice L. Gray

George Mallory

Patrick J. Smith

Martha Markovitz

Melinda Solomon

Erin L. Mahoney

Amy Lucy

John R. McArdle

Joseph M. Pilewski

Albert Faro

Erin Tallarico

Sarah E. Hempstead

References

1. Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, Weiss NS, Goss CH: **Heterogeneity in Survival in Adult Patients With Cystic Fibrosis With FEV1 < 30% of Predicted in the United States**. *Chest* 2017, **151**(6):1320-1328.
2. Martin C, Hamard C, Kanaan R, Boussaud V, Grenet D, Abely M, Hubert D, Munck A, Lemonnier L, Burgel PR: **Causes of death in French cystic fibrosis patients: The need for improvement in transplantation referral strategies!** *J Cyst Fibros* 2016, **15**(2):204-212.
3. Tong A, Chapman JR, Israni A, Gordon EJ, Craig JC: **Qualitative research in organ transplantation: recent contributions to clinical care and policy**. *Am J Transplant* 2013, **13**(6):1390-1399.
4. Barbour RS: **The role of qualitative research in broadening the 'evidence base' for clinical practice**. *J Eval Clin Pract* 2000, **6**(2):155-163.
5. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW *et al*: **The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time**. *J Heart Lung Transplant* 2017, **36**(10):1047-1059.
6. Skelton SL, Waterman AD, Davis LA, Peipert JD, Fish AF: **Applying best practices to designing patient education for patients with end-stage renal disease pursuing kidney transplant**. *Prog Transplant* 2015, **25**(1):77-84.
7. Waterman AD, Morgievich M, Cohen DJ, Butt Z, Chakkera HA, Lindower C, Hays RE, Hiller JM, Lentine KL, Matas AJ *et al*: **Living Donor Kidney Transplantation: Improving Education Outside of Transplant Centers about Live Donor Transplantation--Recommendations from a Consensus Conference**. *Clin J Am Soc Nephrol* 2015, **10**(9):1659-1669.
8. Kerem E, Reisman J, Corey M, Canny GJ, Levison H: **Prediction of mortality in patients with cystic fibrosis**. *N Engl J Med* 1992, **326**(18):1187-1191.
9. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC: **Predictive 5-year survivorship model of cystic fibrosis**. *Am J Epidemiol* 2001, **153**(4):345-352.
10. Aaron SD, Stephenson AL, Cameron DW, Whitmore GA: **A statistical model to predict one-year risk of death in patients with cystic fibrosis**. *J Clin Epidemiol* 2015, **68**(11):1336-1345.
11. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, Stanojevic S: **A contemporary survival analysis of individuals with cystic fibrosis: a cohort study**. *Eur Respir J* 2015, **45**(3):670-679.
12. Belkin RA, Henig NR, Singer LG, Chaparro C, Rubenstein RC, Xie SX, Yee JY, Kotloff RM, Lipson DA, Bunin GR: **Risk factors for death of patients with cystic fibrosis awaiting lung transplantation**. *Am J Respir Crit Care Med* 2006, **173**(6):659-666.
13. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML: **Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality**. *Am J Respir Crit Care Med* 2002, **166**(12 Pt 1):1550-1555.
14. Nkam L, Lambert J, Latouche A, Bellis G, Burgel PR, Hocine MN: **A 3-year prognostic score for adults with cystic fibrosis**. *J Cyst Fibros* 2017, **16**(6):702-708.
15. Milla CE, Warwick WJ: **Risk of death in cystic fibrosis patients with severely compromised lung function**. *Chest* 1998, **113**(5):1230-1234.
16. Quon BS, Psoter K, Mayer-Hamblett N, Aitken ML, Li CI, Goss CH: **Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status**. *Am J Respir Crit Care Med* 2012, **186**(10):1008-1013.

17. Ramos KJ, Quon BS, Psoter KJ, Lease ED, Mayer-Hamblett N, Aitken ML, Goss CH: **Predictors of non-referral of patients with cystic fibrosis for lung transplant evaluation in the United States**. *J Cyst Fibros* 2016, **15**(2):196-203.
18. Rho J, Ahn C, Gao A, Sawicki GS, Keller A, Jain R: **Disparities in Mortality of Hispanic Cystic Fibrosis Patients in the United States: A National and Regional Cohort Study**. *Am J Respir Crit Care Med* 2018.
19. Dolezal L: **The phenomenology of shame in the clinical encounter**. *Med Health Care Philos* 2015, **18**(4):567-576.
20. CR DRHNH: **Reactions to Physcian-Inspired Shame and Guilt**. *Basic and Applied Social Psychology* 2014, **36**:9-26.
21. Oliver KN, Free ML, Bok C, McCoy KS, Lemanek KL, Emery CF: **Stigma and optimism in adolescents and young adults with cystic fibrosis**. *J Cyst Fibros* 2014, **13**(6):737-744.
22. Abbott J, Hart A, Morton A, Gee L, Conway S: **Health-related quality of life in adults with cystic fibrosis: the role of coping**. *J Psychosom Res* 2008, **64**(2):149-157.
23. Abbott J: **Coping with cystic fibrosis**. *J R Soc Med* 2003, **96 Suppl 43**:42-50.
24. Taylor JL, Smith PJ, Babyak MA, Barbour KA, Hoffman BM, Sebring DL, Davis RD, Palmer SM, Keefe FJ, Carney RM *et al*: **Coping and quality of life in patients awaiting lung transplantation**. *J Psychosom Res* 2008, **65**(1):71-79.
25. Miller SM, Shoda Y, Hurley K: **Applying cognitive-social theory to health-protective behavior: breast self-examination in cancer screening**. *Psychol Bull* 1996, **119**(1):70-94.
26. RS HCD: **Shame in Physician-Patient interactions: Patient Perspectives**. *Basic and Applied Social Psychology* 2009, **31**:325-334.
27. Han PK, Moser RP, Klein WM: **Perceived ambiguity about cancer prevention recommendations: relationship to perceptions of cancer preventability, risk, and worry**. *J Health Commun* 2006, **11 Suppl 1**:51-69.
28. Portnoy DB, Han PK, Ferrer RA, Klein WM, Clauser SB: **Physicians' attitudes about communicating and managing scientific uncertainty differ by perceived ambiguity aversion of their patients**. *Health Expect* 2013, **16**(4):362-372.
29. Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, Marshall B, Sabadosa KA, Elborn S, International Committee on Mental H *et al*: **International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety**. *Thorax* 2016, **71**(1):26-34.
30. Dew MA, DiMartini AF, Dobbels F, Grady KL, Jowsey-Gregoire SG, Kaan A, Kendall K, Young QR, Abbey SE, Butt Z *et al*: **The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support**. *J Heart Lung Transplant* 2018, **37**(7):803-823.
31. Robinson W, Waltz DA: **FEV(1) as a guide to lung transplant referral in young patients with cystic fibrosis**. *Pediatr Pulmonol* 2000, **30**(3):198-202.
32. Augarten A, Akons H, Aviram M, Bentur L, Blau H, Picard E, Rivlin J, Miller MS, Katznelson D, Szeinberg A *et al*: **Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients**. *Pediatr Transplant* 2001, **5**(5):339-342.
33. Chen E, Homa K, Goggin J, Sabadosa KA, Hempstead S, Marshall BC, Faro A, Dellon EP: **End-of-life practice patterns at U.S. adult cystic fibrosis care centers: A national retrospective chart review**. *J Cyst Fibros* 2017.
34. Registry CFFP: **2015 Annual Data Report**. *Cystic Fibrosis Foundation* 2016, **Bethesda, Maryland**.
35. K R: **Personal Communication with M Solomon**. September 2018.
36. Ramos K: **Personal Communication with E McKone**. May 2018.

37. Ellaffi M, Vinsonneau C, Coste J, Hubert D, Burgel PR, Dhainaut JF, Dusser D: **One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis**. *Am J Respir Crit Care Med* 2005, **171**(2):158-164.
38. Liou TG, Adler FR, Cox DR, Cahill BC: **Lung transplantation and survival in children with cystic fibrosis**. *N Engl J Med* 2007, **357**(21):2143-2152.
39. Venuta F, Rendina EA, Rocca GD, De Giacomo T, Pugliese F, Ciccone AM, Vizza CD, Coloni GF: **Pulmonary hemodynamics contribute to indicate priority for lung transplantation in patients with cystic fibrosis**. *J Thorac Cardiovasc Surg* 2000, **119**(4 Pt 1):682-689.
40. Tonelli AR, Fernandez-Bussy S, Lodhi S, Akindipe OA, Carrie RD, Hamilton K, Mubarak K, Baz MA: **Prevalence of pulmonary hypertension in end-stage cystic fibrosis and correlation with survival**. *J Heart Lung Transplant* 2010, **29**(8):865-872.
41. Venuta F, Tonelli AR, Anile M, Diso D, De Giacomo T, Ruberto F, Russo E, Rolla M, Quattrucci S, Rendina EA *et al*: **Pulmonary hypertension is associated with higher mortality in cystic fibrosis patients awaiting lung transplantation**. *J Cardiovasc Surg (Torino)* 2012.
42. Vizza CD, Yusen RD, Lynch JP, Fedele F, Alexander Patterson G, Trulock EP: **Outcome of patients with cystic fibrosis awaiting lung transplantation**. *Am J Respir Crit Care Med* 2000, **162**(3 Pt 1):819-825.
43. Scarsini R, Prioli MA, Milano EG, Castellani C, Pesarini G, Assael BM, Vassanelli C, Ribichini FL: **Hemodynamic predictors of long term survival in end stage cystic fibrosis**. *Int J Cardiol* 2016, **202**:221-225.
44. Martin C, Chapron J, Hubert D, Kanaan R, Honore I, Paillasseur JL, Aubourg F, Dinh-Xuan AT, Dusser D, Fajac I *et al*: **Prognostic value of six minute walk test in cystic fibrosis adults**. *Respir Med* 2013, **107**(12):1881-1887.
45. Kadikar A, Maurer J, Kesten S: **The six-minute walk test: a guide to assessment for lung transplantation**. *J Heart Lung Transplant* 1997, **16**(3):313-319.
46. Ciriaco P, Egan TM, Cairns EL, Thompson JT, Detterbeck FC, Paradowski LJ: **Analysis of cystic fibrosis referrals for lung transplantation**. *Chest* 1995, **107**(5):1323-1327.
47. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG *et al*: **A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation**. *J Heart Lung Transplant* 2015, **34**(1):1-15.
48. Liou TG, Adler FR, Cox DR, Cahill BC: **Lung Transplantation and Survival in Children with Cystic Fibrosis**. *N Engl J Med* 2008, **359**(5).
49. Aurora P, Wade A, Whitmore P, Whitehead B: **A model for predicting life expectancy of children with cystic fibrosis**. *Eur Respir J* 2000, **16**(6):1056-1060.
50. Tantisira KG, Systrom DM, Ginns LC: **An elevated breathing reserve index at the lactate threshold is a predictor of mortality in patients with cystic fibrosis awaiting lung transplantation**. *Am J Respir Crit Care Med* 2002, **165**(12):1629-1633.
51. Hayes D, Jr., Tumin D, Daniels CJ, McCoy KS, Mansour HM, Tobias JD, Kirkby SE: **Pulmonary Artery Pressure and Benefit of Lung Transplantation in Adult Cystic Fibrosis Patients**. *Ann Thorac Surg* 2016, **101**(3):1104-1109.
52. Hayes D, Jr., Tobias JD, Mansour HM, Kirkby S, McCoy KS, Daniels CJ, Whitson BA: **Pulmonary hypertension in cystic fibrosis with advanced lung disease**. *Am J Respir Crit Care Med* 2014, **190**(8):898-905.
53. Flores JS, Rovedder PM, Ziegler B, Pinotti AF, Barreto SS, Dalcin Pde T: **Clinical Outcomes and Prognostic Factors in a Cohort of Adults With Cystic Fibrosis: A 7-Year Follow-Up Study**. *Respir Care* 2016, **61**(2):192-199.

54. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM: **Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease**. *Am J Respir Crit Care Med* 2003, **167**(5):735-740.
55. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM: **Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension**. *Am J Respir Crit Care Med* 2009, **179**(7):615-621.
56. Ramos KJ, Somayaji R, Lease ED, Goss CH, Aitken ML: **Cystic fibrosis physicians' perspectives on the timing of referral for lung transplant evaluation: a survey of physicians in the United States**. *BMC Pulm Med* 2017, **17**(1):21.
57. Aris RM, Routh JC, LiPuma JJ, Heath DG, Gilligan PH: **Lung transplantation for cystic fibrosis patients with Burkholderia cepacia complex. Survival linked to genomovar type**. *Am J Respir Crit Care Med* 2001, **164**(11):2102-2106.
58. Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, Stanojevic S: **Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis**. *J Heart Lung Transplant* 2015, **34**(9):1139-1145.
59. Olland A, Falcoz PE, Kessler R, Massard G: **Should cystic fibrosis patients infected with Burkholderia cepacia complex be listed for lung transplantation?** *Interact Cardiovasc Thorac Surg* 2011, **13**(6):631-634.
60. Parize P, Boussaud V, Poinsignon V, Sitterle E, Botterel F, Lefeuvre S, Guillemain R, Dannaoui E, Billaud EM: **Clinical outcome of cystic fibrosis patients colonized by Scedosporium species following lung transplantation: A single-center 15-year experience**. *Transpl Infect Dis* 2017, **19**(5).
61. Chalermskulrat W, Sood N, Neuringer IP, Hecker TM, Chang L, Rivera MP, Paradowski LJ, Aris RM: **Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation**. *Thorax* 2006, **61**(6):507-513.
62. Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Chaparro C, Aaron SD, Whitmore GA, Stanojevic S: **A clinical tool to calculate post-transplant survival using pre-transplant clinical characteristics in adults with cystic fibrosis**. *Clin Transplant* 2017, **31**(6).
63. Vedam H, Moriarty C, Torzillo PJ, McWilliam D, Bye PT: **Improved outcomes of patients with cystic fibrosis admitted to the intensive care unit**. *J Cyst Fibros* 2004, **3**(1):8-14.
64. Snell GI, Bennetts K, Bartolo J, Levvey B, Griffiths A, Williams T, Rabinov M: **Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation**. *J Heart Lung Transplant* 1998, **17**(11):1097-1103.
65. Schwarzenberg SJ, Hempstead SE, McDonald CM, Powers SW, Wooldridge J, Blair S, Freedman S, Harrington E, Murphy PJ, Palmer L *et al*: **Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines**. *J Cyst Fibros* 2016, **15**(6):724-735.
66. Yen EH, Quinton H, Borowitz D: **Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis**. *J Pediatr* 2013, **162**(3):530-535 e531.
67. Hulzebos EH, Bomhof-Roordink H, van de Weert-van Leeuwen PB, Twisk JW, Arets HG, van der Ent CK, Takken T: **Prediction of mortality in adolescents with cystic fibrosis**. *Med Sci Sports Exerc* 2014, **46**(11):2047-2052.
68. de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, Paterson N, Jackson M, Lougheed MD, Kumar V *et al*: **Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis**. *Thorax* 2011, **66**(8):680-685.
69. Flume PA, Yankaskas JR, Ebeling M, Hulsey T, Clark LL: **Massive hemoptysis in cystic fibrosis**. *Chest* 2005, **128**(2):729-738.

70. Vidal V, Therasse E, Berthiaume Y, Bommart S, Giroux MF, Oliva VL, Abrahamowicz M, du Berger R, Jeanneret A, Soulez G: **Bronchial artery embolization in adults with cystic fibrosis: impact on the clinical course and survival**. *J Vasc Interv Radiol* 2006, **17**(6):953-958.
71. Town JA, Aitken ML: **Deaths Related to Bronchial Arterial Embolization in Patients With Cystic Fibrosis: Three Cases and an Institutional Review**. *Chest* 2016, **150**(4):e93-e98.
72. Raghavan D, Gao A, Ahn C, Kaza V, Finklea J, Torres F, Jain R: **Lung transplantation and gender effects on survival of recipients with cystic fibrosis**. *J Heart Lung Transplant* 2016, **35**(12):1487-1496.
73. Reid DW, Blizzard CL, Shugg DM, Flowers C, Cash C, Greville HM: **Changes in cystic fibrosis mortality in Australia, 1979-2005**. *Med J Aust* 2011, **195**(7):392-395.
74. Sell JL, Bacchetta M, Goldfarb SB, Park H, Heffernan PV, Robbins HA, Shah L, Raza K, D'Ovidio F, Sonett JR *et al*: **Short Stature and Access to Lung Transplantation in the United States. A Cohort Study**. *Am J Respir Crit Care Med* 2016, **193**(6):681-688.
75. Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL: **Pneumothorax in cystic fibrosis**. *Chest* 2005, **128**(2):720-728.
76. CA WNFSMNTATECRDRBKEJBESPM: **WS18.2 The transition towards lung transplant for cystic fibrosis in the United Kingdom**. *Journal of Cystic Fibrosis* 2018, **17**:S33.
77. A DVPAP-BDKRKMLR: **WS18.4 Evaluation of transplantation information delivered to patients and their relatives by the professionals from cystic fibrosis centres and transplant centres and from transplanted peer-patients in France**. *Journal of Cystic Fibrosis* 2018, **17**:S33-34.