

# Regence

Medical Policy Manual

Transplant, Policy No. 08

## ***Lung and Lobar Lung Transplant***

**Effective:** June 1, 2023

**Next Review:** March 2024

**Last Review:** April 2023

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

A lung transplant consists of replacing all or part of diseased lungs with healthy lung(s). Transplantation is an option for patients with end-stage lung disease.

### **MEDICAL POLICY CRITERIA**

- I. Lung transplantation may be considered **medically necessary** for carefully selected patients with irreversible, progressively disabling, end-stage pulmonary disease unresponsive to maximum medical therapy.
- II. A lobar lung transplant from a living or deceased donor may be considered **medically necessary** for carefully selected patients with end-stage pulmonary disease.
- III. Lung or lobar lung retransplantation after a failed lung or lobar lung transplant may be considered **medically necessary** in patients who meet either criterion I or II.
- IV. Lung or lobar lung transplantation is considered **not medically necessary** in all other situations.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

End-stage pulmonary disease may include, but is not limited to, the following diagnoses:

- Alpha-1 antitrypsin deficiency
- Bilateral bronchiectasis
- Bronchiolitis obliterans
- Bronchopulmonary dysplasia
- Chronic obstructive pulmonary disease
- Cystic fibrosis (both lungs to be transplanted)
- Eisenmenger's syndrome
- Emphysema
- Eosinophilic granuloma
- Idiopathic/interstitial pulmonary fibrosis
- Lymphangiomyomatosis
- Postinflammatory pulmonary fibrosis
- Primary pulmonary hypertension
- Pulmonary hypertension due to cardiac disease
- Recurrent pulmonary embolism
- Sarcoidosis
- Scleroderma

## LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant

## CROSS REFERENCES

1. [Heart/Lung Transplant](#), Transplant, Policy No. 3

## BACKGROUND

End-stage lung disease may be the consequence of a number of different conditions. The most common indications for lung transplantation are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, alpha-1 antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. Prior to the consideration for transplant, patients should be receiving maximal medical therapy, including oxygen supplementation, or surgical options, such as lung-volume reduction surgery for COPD. Lung or lobar lung transplantation is an option for patients with end-stage lung disease despite these measures.

A lung transplant refers to single-lung or double-lung replacement. In a single-lung transplant, only one lung from a deceased donor is provided to the recipient. In a double-lung transplant, both the recipient's lungs are removed and replaced by the donor's lungs. In a lobar transplant, a lobe of the donor's lung is excised, sized appropriately for the recipient's thoracic dimensions, and transplanted. Donors for lobar transplant have primarily been living-related

donors, with one lobe obtained from each of two donors (e.g., mother and father) in cases for which bilateral transplantation is required. There are also cases of cadaver lobe transplants. Combined lung-pancreatic islet cell transplant is being studied for patients with cystic fibrosis.<sup>[1]</sup>

Potential recipients who are 12 years of age and older are ranked according to the Lung Allocation Score (LAS).<sup>[2]</sup> A score may range between 1 and 100 and incorporates predicted survival after transplantation and predicted survival on the waiting list; the LAS takes into consideration the patient's disease and clinical parameters. Waiting list incorporates the LAS, geography, and blood type classifications. Children younger than age 12 years old receive a priority for lung allocation. Under this system, children younger than 12 years old with respiratory lung failure and/or pulmonary hypertension who meet criteria are considered "priority 1" and all other candidates in the age group are considered "priority 2." A lung review board has the authority to adjust scores on appeal for adults and children.

## EVIDENCE SUMMARY

Due to the nature of the population, there are no randomized controlled trials (RCTs) that compare lung transplantation with alternatives. Systematic reviews are based on case series and registry data. The extant RCTs compare surgical technique, infection prophylaxis, or immunosuppressive therapy and are not germane to this policy. Therefore, the following is a summary of the evidence based on registries, case series, and expert opinion.

### **SURVIVAL**

The Registry of the International Society for Heart and Lung Transplantation (ISHLT) contains data from 49,453 adult recipients who received lung transplantation (including lung retransplantation) through June 30, 2015, at 134 transplant centers.<sup>[3]</sup> A total of 55,795 lung transplants were performed, of which 53,522 (95.9%) were primary transplants and 2,273 (4.1%) were retransplants. The overall median survival of patients who underwent lung transplantation was 5.8 years. Estimated unadjusted survival rates were 89% at three months, 80% at one year, 65% at five years, and 32% at 10 years. Patients who survived a year after primary transplantation had a median survival of 8.0 years. In the first 30 days after transplantation, the major reported causes of mortality were graft failure (24.5%) and non-cytomegalovirus (CMV) infections (19.1%), while non-CMV infections became the major cause of death for the remainder of the first year. Beyond the first year, the most common reported causes of mortality were obstructive bronchiolitis/bronchiolitis obliterans syndrome (OB/BOS), graft failure, and non-CMV infections. Beyond 10 years post-transplant, the major causes of mortality were OB/BOS (21.5%), non-CMV infection (16.5%) and non-lymphoma malignancy (13.7%).

The ISHLT registry contains a total of 2,229 pediatric lung transplants performed through 2014.<sup>[4]</sup> Most transplants (73%) were done in older children between the ages of 11 to 17 years. Median survival in children who underwent lung transplantation was 5.4 years, similar to survival in adults (mean survival, 5.7 years). However, median survival in children was lower (2.2 years) than in adults (5.6 years) for single-lung transplants.

Black (2014) published results from an analysis of lung transplants using data from the United Network for Organ Sharing's (UNOS) Scientific Registry of Transplant Recipients from 1994 to June 2012.<sup>[5]</sup> The goal of the analysis was to evaluate how survival was affected in patients who had a high lung allocation score (LAS) and received a single versus a double lung

transplant. In all, there were 8,778 patients identified; however, just 8,050 had a LAS less than 75, and 728 has a LAS greater than or equal to 75. Kaplan-Meier survival curves stratified by high and low LAS, and by single versus double lung transplants, showed a significant decrease in survival ( $p < 0.001$ ) in those with a high LAS who received a single lung transplant when compared with those with a high LAS who received a double lung transplant. The authors, that despite a higher operative morbidity, patients who had a high LAS did substantially better in terms of survival if two lungs were transplanted rather than only one, with a larger difference in survival than for patients with a lower LAS.

Yu (2019) compared double-lung with single-lung transplantations for outcomes of survival, pulmonary function, surgical indicators, and complications in a meta-analysis of 30 studies ( $n = 1,980$  recipients of single-lung transplants and  $n = 2,112$  recipients of double-lung transplants).<sup>[6]</sup> Overall survival, in-hospital mortality, and postoperative complications besides bronchiolitis obliterans syndrome were similar between the two groups. Recipients of double-lung transplants had lower rates of bronchiolitis obliterans syndrome, better postoperative lung function, improved long-term survival, while recipients of single-lung transplants spent less time in surgery, postoperative intensive care unit, and postoperative hospital stay.

Thabut (2009) reported on a comparison of patients undergoing single- and double-lung transplantation for idiopathic pulmonary fibrosis.<sup>[7]</sup> A retrospective review was conducted of 3,327 patients with data in the UNOS registry. More patients underwent single-lung as compared to double-lung transplant (64.5 vs. 35.5%, respectively). Median survival time was greater for the double-lung group at 5.2 years (95% CI 4.3 to 6.7 years) versus 3.8 years (95% CI 3.6 to 4.1 years,  $p < 0.001$ ). After adjustment for baseline differences, however, survival times were not statistically different. The authors concluded that overall survival did not differ between the two groups: single-lung transplants offered improved short-term survival but long-term harm, whereas double-lung transplant increased short-term harm but was associated with a long-term survival benefit. Later, Black (2014) reported on the LAS and single- versus double-lung transplant in 8,778 patients (8,050 had an LAS less than 75 and 728 had an LAS of 75 or higher).<sup>[5]</sup> A significant decrease in survival was seen in single-lung transplant patients with a high LAS compared with double-lung transplant patients with a high LAS, even though operative morbidity was higher ( $p < 0.001$ ).

Hayanga (2016) analyzed lung transplantation data from the UNOS registry between 2005 and 2013.<sup>[8]</sup> Survival was analyzed in relation to the annual volume of lung transplants performed at each center: less than 20, 20-29, 30-39, and 40 or more. During the study period, 13,506 adults underwent lung transplantation. Approximately 40% of the transplants were performed in centers with a volume of 40 or more, with the remaining transplants spread relatively equally across lower volume center groups. Both one- and five-year patient survival tended to increase with increasing volume, but the authors noted that it was a relatively small effect.

Kistler (2014) reported on a systematic review of the literature on waitlist and posttransplant survival for idiopathic pulmonary fibrosis.<sup>[9]</sup> Estimated median survival of idiopathic pulmonary fibrosis patients posttransplantation is estimated at 4.5 years and is lower than other underlying pretransplant diagnoses. From ISHLT and the Organ Procurement and Transplantation Network (OPTN) data, one-year survival ranged from 75% to 81%; three-year, 59% to 64%, and five-year, 47% to 53%. Limited data were available on posttransplant morbidity outcomes.

Taimh (2016) reported on post-lung transplant survival in 695 patients with pulmonary sarcoidosis in the U.S.<sup>[10]</sup> Survival in this group was similar to that of non-sarcoid lung recipients, and in a multivariate analysis, sarcoidosis was not associated with higher mortality. In the sarcoidosis group, LAS and double lung transplantation were both associated with improved survival.

## **PATIENT SELECTION**

Based on concern that the LAS may prioritize lung transplant candidates with a poor expected survival benefit from the procedure, Li (2019) analyzed data from the UNOS registry (n=21,157) to determine whether there was a LAS threshold above which the score did not predict increasing survival benefit.<sup>[11]</sup> The results of this analysis indicated that the greatest benefit was seen for recipients with scores between 70 and 79 (n=365), with a hazard ratio of death after undergoing transplantation relative to remaining on the waitlist of 0.2 (95% CI 0.1 to 0.3). Survival for patients with LAS scores above this range was not significantly increased. The authors noted that the survival benefit threshold for patients with cystic fibrosis was quite a bit lower, at a score of approximately 50.

Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation, and 426 who underwent primary lung transplantation between 2005 and 2010.<sup>[12]</sup> Patients on the waitlist who had a higher LAS had a higher rate of mortality (p<0.001). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival (p=0.05) but not late posttransplant survival (p=0.4). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality (p=0.12).

Russo (2011) analyzed a dataset of 6,082 patients who received a lung transplant between May 4, 2005 and May 4, 2009 in order to describe outcomes and estimate the survival benefit based upon patient lung allocation score.<sup>[13]</sup> Authors found that although lower priority patients comprise the majority of transplants, mid-priority groups with LAS of 50 to 79, seemed to achieve the greatest survival benefit from transplantation (2.81 to 3.49 years). Patients with the highest and lowest LAS score achieved the least survival benefit; however, it was noted that patients with high allocation scores were expected to have worse survival and that patients with lower LAS had the lowest risk of death on the waiting list. Data suggested that transplant centers may be justified in considering patients for lung transplantation who had a mid-range allocation scores before patients with the highest and lowest scores.

Yusen (2010) reviewed the effect of the LAS on lung transplantation by comparing statistics for the period before and after its implementation in 2005.<sup>[14]</sup> Other independent changes in clinical practice, which may affect outcomes over the same period of time, include variation in immunosuppressive regimens, an increased supply of donor lungs, changes in diagnostic mix, and increased consideration of older recipients. Deaths on the waiting list declined following implementation of the LAS system, from approximately 500 per 5,000 patients to 300 per 5,000 patients. However, it is expected that implementation of the LAS affected patient characteristics of transplant applicants. One-year survival post-transplantation did not improve after implementation of the LAS system: patient survival data before and after are approximately 83%. More recently, Shafii (2014) reported on a retrospective evaluation of the LAS and mortality in 537 adults listed for lung transplantation and 426 who underwent primary lung transplantation between 2005 and 2010.<sup>[12]</sup> Patients on the waitlist who had a higher LAS

had a higher rate of mortality ( $p < 0.001$ ). In the highest quartile of LAS, ranging from 47 to 95, within one year of listing, there was a 75% mortality rate. Higher LAS was also associated with early posttransplant survival ( $p = 0.05$ ) but not late posttransplant survival ( $p = 0.4$ ). When other predictive factors of early mortality were accounted for, pretransplant LAS was not independently related to posttransplant mortality ( $p = 0.12$ ).

Gries (2010) published results from a study on pre-transplant characteristics of 10,128 patients from the Organ Procurement and Transplantation Network (OPTN) database were examined to understand how well LAS post-transplant survival model parameters predict one- and five-year survival.<sup>[15]</sup> Authors concluded that the LAS system and pre-transplant characteristics in general did not predict long term one- or five-year survival better than chance.

Kozower (2008) performed a retrospective cohort study using data from five academic medical centers to evaluate the impact of the LAS on short-term outcomes after lung transplantation.<sup>[16]</sup> (The LAS was implemented in May 2005 by the OPTN.) This score changed lung allocation from a system based on waiting time to an algorithm based on the probability of survival for one year on the transplant list and survival one-year post-transplantation. Results were compared for 170 patients who received transplants based on the new lung allocation scores (May 4, 2005 to May 3, 2006) with those of 171 patients who underwent transplants the preceding year before implementation of the scoring system. Waiting time decreased from 681 to 445.6 days ( $p < 0.001$ ). Recipient diagnoses changed, with an increase (15% to 25%) in idiopathic pulmonary fibrosis cases and decreases in emphysema (46% to 34%) and cystic fibrosis (23% to 13%). Hospital mortality and one-year survival were the same between groups (5.3% vs. 5.3% and 90% vs. 89%, respectively). Presumably due to increased severity of illness, the incidence of primary graft dysfunction and postoperative intensive care unit length of stay increased in the year after implementation of the scoring system; graft dysfunction grew from 14.8% (24/170) to 22.9% (39/171); ( $p = 0.04$ ) and length of stay rose from 5.7 to 7.8 days.

## **PEDIATRIC CONSIDERATIONS**

A retrospective cohort study from 150 centers worldwide was conducted by Nelson (2021).<sup>[17]</sup> The results compared outcomes of 2232 pediatric patients with or without cystic fibrosis that underwent lung transplantation between 1990 and 2017. The primary outcomes were all-cause mortality and graft failure at timepoints of 30 days, one year, five years, and 10 years. The proportion of patients undergoing lung transplantation without cystic fibrosis is increasing where nearly half of primary pediatric lung transplantations are performed for other indications. These patients without cystic fibrosis were younger, more commonly receiving intensive care, were on inotropes and/or extracorporeal membrane oxygenation (ECMO). Mortality was higher for non-cystic fibrosis patients after 30 days compared to patients with cystic fibrosis. A diagnosis of pulmonary arterial hypertension was also a risk factor for pediatric patients without cystic fibrosis at one and five years. However, long-term survival was higher in these patients without cystic fibrosis comparatively.

Paraskeva (2018) analyzed survival rates of adolescent lung transplant recipients using data from the ISHLT registry.<sup>[18]</sup> Patients between 10 and 24 years old represented 9% of the registry data ( $n = 2,319$ ) and they were compared with both old and young cohorts. Overall survival in the adolescent cohort was 65% at three years, which was similar to that observed in adults between 50 and 65 years of age, but significantly lower than the three-year survival

rate among the pediatric subgroup (73%,  $p=0.006$ ) and adults 25 to 34 years old (75%,  $p<0.001$ ) and 35 to 49 years old (71%,  $p<0.001$ ). Within the adolescent group, patients between 15 and 19 years of age had the poorest survival rates at three years (59%) compared with 10- to 14-year old patients (73%,  $p<0.001$ ) and 20- to 24-year old patients (66%,  $p<0.001$ ). The registry study was biased toward inclusion of North American data and potential data entry errors or missing data. There were no data reported on cause of mortality, differences in regimens, or rates of graft dysfunction between the groups.

Benden (2012) reviewed pediatric lung transplants that have been reported to the international registry.<sup>[19]</sup> Pediatric patients are defined as those younger than 18 years of age. The authors noted an increase in the number of pediatric lung transplants in recent years; there were 126 transplants in 2010 compared to 73 in 2000. In contrast to adult patients, the most common indication for pediatric patients was cystic fibrosis, accounting for 54% of lung transplants in 6- to 11-year-olds and 72% of lung transplants in 12- to 17-year-olds that occurred between 1990 and June 2011. Survival has improved in the recent era, and five-year survival is not significantly different from adult recipients. The half-life, estimated time at which 50% of recipients have died, was 4.7 years for children and 5.3 years for adults. For children receiving allografts between 2002 and June 2010, the five-year survival rate was 54% and seven-year survival was 44%. Patients aged 1 to 11 years had a significantly better survival rate than those between the ages of 12 and 17 years (half-life of 6.2 years and 4.3 years, respectively). In the first year after lung transplantation, non-CMV infection and graft failure were the two leading causes of death. Bronchiolitis obliterans syndrome was the major cause of death beyond three years after transplantation.

Moreno (2016) compared survival and clinical outcomes in pediatric and adult lung transplantation for cystic fibrosis at a single institution.<sup>[20]</sup> There were 120 patients included in the study: 50 children and 70 adults, who underwent 111 bilateral, four lobar, four combined and one unilateral lung transplant. Overall survival for children at five, ten, and 15 years was 57, 45, and 35% vs, 67, 55, and 43% for adults, respectively ( $p=0.32$ ). Pediatric patients were significantly more likely than adults to have used cardiopulmonary bypass (56% vs. 28%,  $p=0.002$ ), have acute rejection episodes ( $1.4 \pm 0.7$  vs.  $1.2 \pm 0.8$ ,  $p=0.004$ ), and stay longer in intensive care ( $20 \pm 19$  vs.  $10 \pm 9$  days,  $p=0.006$ ). The authors noted that pediatric cystic fibrosis patients presenting for lung transplant tend to have a worse status than adult patients, which might explain some of these differences.

Mangiameli (2016) reported on outcomes of pediatric lung transplantation at a center in France, with a focus on sex matching of donors and recipients.<sup>[21]</sup> In this study, which included 58 patients below age 18, the 30-day mortality was 10% and survival at one, five, and 10 years was 81%, 60%, and 57%, respectively. Among these patients, female sex and sex mismatching were associated with poor prognosis, with female recipients of male-donated organs having particularly poor outcomes.

A study by Fraser (2019) used information from the UNOS database to examine the role of size mismatch in preadolescent lung transplantation.<sup>[22]</sup> There were 540 patients included in the analysis, which found that one-year mortality was higher for patients with height and weight mismatching, and for predictive total lung capacity ratios less than 0.9 ( $p=0.017$ )

## **POTENTIAL CONTRAINDICATIONS**

### **Malignancy**

Concerns regarding a potential recipient's history of cancer have been based on the observation of significantly increased incidence of cancer in kidney transplant patients.<sup>[23]</sup> For renal transplant patients who had a malignancy treated prior to transplant, the incidence of recurrence ranged from zero to more than 25%, depending on the tumor type.<sup>[24, 25]</sup> However, it should be noted that the availability of alternative treatment strategies informs recommendations for a waiting period following high-risk malignancies: in renal transplant, a delay in transplantation is possible due to dialysis; end-stage lung disease patients may not have an option to defer.

A 2012 study reported on outcomes in patients with lung cancer who were lung transplant recipients.<sup>[26]</sup> Ahmad and colleagues identified 29 individuals in the UNOS database who underwent lung transplantation for advanced bronchoalveolar carcinoma (BAC). These patients represented 0.13% of the 21,553 lung transplantations during the study period. BAC and general lung transplant recipients had similar survival rates: the 30-day mortality rate was 7% versus 10% ( $p=0.44$ ) and five-year survival rate was 50% versus 57% ( $p=0.66$ ), respectively.

### **Human Immunodeficiency Virus (HIV)**

The current Organ Procurement Transplantation Network (OPTN) policy permits HIV-positive transplant candidates.<sup>[27]</sup> The 2020 US Public Health Service guideline also allows for transplantations in HIV-positive recipients with proper screenings and effective regimens for HIV infections.<sup>[28]</sup>

### **Other Infections**

Infection with *Burkholderia cenocepacia* is associated with increased mortality in some transplant centers, a factor that may be considered when evaluating overall risk for transplant survival.<sup>[29]</sup>

A 2016 analysis of international registry data found that non-CMV infection is a major cause of mortality within 30 days of lung transplant in adults.<sup>[3]</sup> A total of 655 (19%) of 3,424 deaths after transplants between January 1990 and June 2015 were due to non-CMV infection. Only three (0.1%) of the deaths were due to CMV infection.

Wojarski (2018) assessed the impact of bacterial infection on mortality in 97 lung transplant patients from a single center between 2004 and 2016.<sup>[30]</sup> The mean hospitalization time was 57 days, and 67 patients had a total of 120 episodes of bacterial infection. The most common sources of infection were *Pseudomonas aeruginosa* (27%), followed by *Acinetobacter baumannii* (21%), and *Stenotrophomonas maltophilia* (11%). There were 39 patients who developed bronchiolitis obliterans syndrome. *A. baumannii* infection was associated with decreased survival, while treatment with mammalian target of rapamycin inhibitors was linked to increased survival.

Lobo (2013) reported on 13 lung transplant patients with *Mycobacterium abscessus* in cystic fibrosis.<sup>[31]</sup> Survival rates were 77%, 64% and 50% after transplant at one, three, and five years, respectively. These results were not significantly different when compared to 154 cystic fibrosis patients treated with lung transplantation who did not have *M. abscessus* ( $p=0.8$ ).

Shields (2012) reported on infections in 596 consecutive lung transplant recipients treated at a single center occurring in the first 90 days after transplantation.<sup>[32]</sup> A total of 109 patients



(18%) developed 138 *Staphylococcus aureus* (*S. aureus*) infections. The most common type of infection was pneumonia (66 of 138, 48%) followed by tracheobronchitis (36 of 138, 26%) and bacteremia (17 of 138, 12%). Thirteen of 109 (12%) of patients with *S. aureus* infection died within 90 days of the onset of infection. The one-year mortality rate was higher for patients with *S. aureus* pneumonia (19 of 66, 29%) but not *S. aureus* tracheobronchitis (8 of 36, 22%) compared with uninfected patients (85 of 487, 17%).

Pinney (2011) published results from a retrospective review of invasive fungal infection rates in lung transplantation patients without cystic fibrosis treated at a single center.<sup>[33]</sup> Patients were followed for a median of 34 months. Invasive fungal infections were identified in 22 of 242 (9.1%) patients. *Aspergillus* infections were most common, occurring in 11 of 242 (4.5%) of patients. There were also seven cases (3%) of *Candida* infection. Survival rates did not differ significantly in patients with invasive fungal infections compared to the entire cohort of patients. For example, three-year survival was 50% among patients with invasive fungal infection and 66% in the entire cohort (p=0.66). The authors did not compare survival in patients with invasive fungal infections to survival only in those without invasive fungal infections.

In a study published by Murray (2008), multivariate Cox survival models assessing hazard ratios (HRs) were applied to 1,026 lung transplant candidates and 528 transplant recipients.<sup>[34]</sup> Of the transplant recipients, 88 were infected with *Burkholderia*. Among transplant recipients infected with *Burkholderia cenocepacia*, only those infected with nonepidemic strains (n=11) had significantly greater post-transplant mortality than uninfected patients (HR 2.52, 95% CI 1.04 to 6.12, p=0.04). Transplant recipients infected with *Burkholderia gladioli* (n=14) also had significantly greater post-transplant mortality than uninfected patients (HR 2.23, 95% CI 1.05 to 4.74, p=0.04). When adjustments for specific species/strains were included, lung allocation scores of *Burkholderia multivorans*-infected transplant candidates were comparable to uninfected candidate scores, and scores for patients infected with non-epidemic *B. cenocepacia* or *B. gladioli* were lower. In a smaller study of 22 patients colonized with *Burkholderia cepacia* complex who underwent lung transplantation in two French centers, the risk of death by univariate analysis was significantly higher for the eight patients infected with *B. cenocepacia* than for the other 14 colonized patients (11 of whom had *B. multivorans*).<sup>[35]</sup>

### **Coronary Artery Disease (CAD)**

Castleberry (2013) reported on a retrospective cohort study of lung transplantation with concurrent CAB or preoperative percutaneous coronary intervention (PCI).<sup>[36]</sup> Out of 898 lung transplants performed during the period between 1997 and 2010, 49 patients also had concurrent CAB and 38 patients had preoperative PCI. All of the intervention groups, including revascularization, had similar rates of perioperative mortality, overall unadjusted survival and adjusted HR for cumulative risk of death. Postoperative major adverse cardiac event rates were also similar among groups, although postoperative length of stay, intensive care unit time and need for ventilator support increased in patients receiving concurrent CAB with lung transplantation.

Sherman (2011) reported on outcomes in 27 patients with CAD at a single center who underwent lung transplantation and coronary revascularization.<sup>[37]</sup> Patients needed to be otherwise considered good candidates for transplantation and have discrete coronary lesions (at least 50% in the left main artery or at least 70% in other major vessels) and preserved

ejection fraction. Thirteen patients had single-lung transplantation and 14 had double-lung transplantation. Outcomes were compared with a control group of 81 patients without CAD who underwent lung transplantation; patients were matched for age, diagnosis, lung allocation score and type of procedure. During a mean follow-up of three years, nine of 27 (33%) patients with CAD and 28 of 81 (35%) without CAD died ( $p=0.91$ ). Bronchiolitis obliterans and infection were the primary causes of death. There was no significant difference between groups in a composite outcome of adverse cardiac events (defined as acute coronary syndrome, redo revascularization or hospital admissions for congestive heart failure),  $p=0.80$ .

## **LOBAR LUNG TRANSPLANTATION**

Several case series have reported outcomes after lobar lung transplants in both children and adults.

Eberlein (2017) published a systematic review of studies on lobar lung transplantation from deceased donors.<sup>[38]</sup> Reviewers identified nine studies comparing outcomes after lobar lung or lung transplant, all of which were single-center retrospective cohort studies. Seven studies were conducted in Europe, one in Australia, and one in North America. One-year survival reported in individual studies ranged from 50% to 100% after lobar lung transplant and from 72% to 88% after conventional lung transplant. In a pooled analysis of data from eight studies, lobar lung transplant recipients ( $n=284$ ) had a significantly higher risk of one-year mortality than lung transplant recipients ( $n=2,777$ ) (relative risk [RR] 1.85, 95% CI 1.52 to 2.25,  $p<0.001$ ,  $I^2=0\%$ ).

Date (2014) reported on a retrospective study comparing 42 living-donor lobar lung transplants and 37 cadaveric lung transplants.<sup>[39]</sup> Survival rates at one and three years were not significantly different between the groups (89.7 and 86.1% vs 88.3 and 83.1%, respectively,  $p=0.55$ ), despite living-donor lobar lung transplant patients having poorer health status preoperatively.

Slama (2014) reported on a comparison of outcomes in 138 cadaveric lobar lung transplants (for size discrepancies) to 778 patients who received cadaveric whole-lung transplants, 239 of whom had downsizing by wedge resection of the right middle lobe and/or the left lingula.<sup>[40]</sup> Survival in the lobar lung transplant group at one and five years was 65.1% and 54.9% versus 84.8% and 65.1% in the whole lung and downsized by wedge resection group ( $p<0.001$ ). The lobar lung transplantation group experienced significantly inferior early postoperative outcomes, but in patients who were successfully discharged, survival rates were similar to standard lung transplantation ( $p=0.168$ ).

In 2012, a program in Japan reported on 14 critically ill patients who had undergone single living-donor lobar lung transplants; there were ten children and four adults.<sup>[41]</sup> Patients were followed for a mean 45 months. The three-year survival rate was 70% and the five-year survival was 56%. Severe graft dysfunction occurred in four patients. Mean forced vital capacity (FVC) was found to be lower in patients experiencing severe graft dysfunction compared to the other patients, mean FVC was 54.5% and 66.5%, respectively. The authors stated that this suggests size mismatching in the patients with severe graft dysfunction. The same year, Inci (2012) published data on 23 patients in Switzerland who received bilateral lobar lung transplants.<sup>[42]</sup> The mean age was 41 years (range 13 to 66 years). Survival at one and two years was 82% and 64%, respectively; survival rates were comparable with 219 patients who underwent bilateral lung transplantation during the same period ( $p=0.56$ ).

A review article by Date (2015) stated that, as of 2011, approximately 400 living-donor lobar lung transplants have been performed worldwide.<sup>[39]</sup> Procedures in the U.S. decreased after 2005 due to changes in the lung allocation system. The author stated that size matching between donor and recipient is important and that, to some extent, size mismatching (oversized or undersized grafts) can be overcome by adjusting surgical technique.

Several studies reported on lobar lung transplantation from living donors. For example, Barr (2005) reported on experience performing living donor lobar lung transplants in the U.S.<sup>[43]</sup> Ninety patients were adults and 43 were children. The primary indication for transplantation (86%) was cystic fibrosis. At the time of transplantation, 67% of patients were hospitalized and 20% were ventilator dependent. Overall recipient actuarial survival at one, three and five years was 70%, 54% and 45%, respectively. There was not a statistically significant difference in actuarial survival between adults and children who underwent transplantation. Moreover, survival rates were similar to the general population of lung transplant recipients. The authors also reported that rates of postoperative pulmonary function in patients surviving more than three months post-transplant were comparable to rates in cadaveric lung transplant recipients.

## **RETRANSPLANTATION**

Registry data and case series reports have demonstrated favorable outcomes with lung retransplantation in certain populations, such as in patients who meet criteria for initial lung transplantation.<sup>[44-47]</sup>

OPTN reported data on lung transplants performed between 2008 and 2015.<sup>[48]</sup> Patient survival rates after repeat transplants were lower than primary transplants, but a substantial number of patients survived. For example, one-year patient survival was 87.9% (95% CI 87.2% to 88.7%) after a primary lung transplant and 76% (95% CI 70.9% to 80.2%) after a repeat transplant. Five-year patient survival was 55.9% (54.7% to 57.2%) after a primary lung transplant and 33.8% (28.5 to 39.1%) after repeat transplant.

The ISHLT registry contains data on 2,273 retransplantations performed through June 2015 (4.4% of all lung transplantations during this period).<sup>[3]</sup> The major causes of death in the first 30 days after retransplantation were graft failure and non-CMV infection, followed by multiorgan failure, cardiovascular causes and technical factors related to the transplant procedure. Beyond the first year, the most common reported causes of mortality were OB/BOS, graft failure, and non-CMV infections.

Biswas Roy (2018) published a single-center retrospective study comparing survival outcomes in 29 patients who received retransplantation for chronic lung allograft dysfunction with 390 patients receiving primary lung transplant at the same center.<sup>[49]</sup> Patients receiving retransplantation had significantly higher use of extracorporeal membrane oxygenation support for severe primary graft dysfunction ( $p=0.019$ ) and underwent cardiopulmonary bypass and re-exploration for bleeding ( $p=0.019$ ) more frequently than patients receiving primary transplantation ( $p=0.029$ ). At one-year follow-up, 89.7% of primary transplant patients were living, as were 89.2% of retransplantation patients. At five-year follow-up, a greater percentage of the retransplantation group had survived, compared with the primary transplantation group (64.3% vs 58.2%), although the difference was not statistically significant. While high LAS and extended hospital length of stay were both identified as independent mortality risk factors, retransplantation was not (HR 1.58, 95% CI 0.31 to 8.08,  $p=0.58$ ). Study limitations included its single-center, retrospective design, the potential selection bias for younger patients, and the

small size of the retransplantation group. Further, follow-up data at three and five years were incomplete for some patients, and patients who were refused retransplantation were not considered in the analyses. However, for appropriately selected patients, retransplantation after chronic lung allograft dysfunction resulted in one- and five-year survival rates comparable to those seen after primary lung transplantation.

Thomas (2015) published results from a retrospective study that compared patient survival after lung retransplantation (LRTx) to primary lung transplantation (LPTx) in the U.S. using data from the UNO registry between 2004 and 2013.<sup>[50]</sup> A total of 582 LRTx and 13,673 LPTx recipients were included in the analysis. The median survival after LRTx was 2.6 years compared with 5.6 years after LPTx. One-year, three-year, and five-year survival rates were, respectively, 71.1%, 46.3%, and 34.5% for LRTx, and 84.3%, 66.5%, and 53.3% for LPTx ( $p < 0.001$ ). On multivariate analysis, patients who had LRTx after a greater than one-year interval survived longer (RR 0.53, 95% CI 0.34% to 0.88%,  $p = 0.008$ ). Lower survival was associated with single-lung transplantations (RR 1.49, 95% CI 1.06% to 2.07%,  $p = 0.021$ ), transplantations done between 2009 and 2013 (RR 1.40, 95% CI 1.01% to 1.94%,  $p = 0.041$ ), multiple retransplantations (RR 2.55, 95% CI 1.14% to 5.72%,  $p = 0.023$ ), and recipients requiring pre-transplantation ventilator support.

Kilic (2013) evaluated data on 390 adult lung retransplantation patients from the UNOS database.<sup>[45]</sup> Patients received lung retransplantation during the period May 2005 to December 2010, which was after the LAS selection criteria were implemented. Patients with reduced functional status were found to have poorer outcomes than patients with better functional status prior to retransplantation. Using the Karnofsky scale to stratify patients into functional status groups, the authors found the overall one-year survival of 56% for patients requiring total assistance before retransplantation was significantly lower than the overall one-year survival of 82% for patients who only required some assistance before retransplantation ( $p < 0.001$ ). The one-year mortality rate after risk adjustment was also increased significantly for patients requiring total assistance prior to retransplantation (odds ratio 3.72,  $p = 0.02$ ). While additional patient selection criteria may be useful for lung retransplantation, current LAS criteria are now used.

## PRACTICE GUIDELINE SUMMARY

### INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION

In 2021, the International Society for Heart and Lung Transplantation published updated consensus-based guidelines on the selection of lung transplant candidates.<sup>[51]</sup>

"Lung transplantation should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed.
2. High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function."

The guideline also notes risk factors to be considered in the evaluation of transplant candidates, along with pediatric and disease-specific considerations.

The 2021 guideline update briefly addressed lung **retransplantation**, with the consensus statement noting that "The outcomes after re-transplants are inferior compared to first lung transplants, particularly if the re-transplant is done within the first year after the original transplant or for patients with restrictive allograft syndrome (RAS) [...] In the pre-transplant evaluation of such patients, particular emphasis should be focused on understanding the possible reasons for the graft failure, such as alloimmunization, poor adherence, gastroesophageal reflux, or repeated infections".

In 2015, the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation (ISHLT) published an update to their 2006 consensus-based guidelines on selection of lung transplant candidates.<sup>[52, 53]</sup> The guidelines state:

“... there is general agreement that referral to a lung transplant program should occur early in patients who have a lung disease that is amenable to transplantation. None of the parameters listed in this document informing on the timing of referral or listing should be used in isolation. Instead, the entire clinical situation of the patient should be considered. However, early referral does give the transplant program maximal flexibility in performing the formal evaluation and in making the second more important step—placing the patient on the active waiting list. Listing a patient for a lung transplant is an explicit acknowledgement that a patient has a limited life expectancy without a transplant and an expectation that the risk-to-benefit ratio favors lung transplantation rather than conventional medical treatment.”

For lung retransplantation, the guidelines state:

“Lung retransplantation accounts for a small percentage of lung transplants performed annually. However, its frequency has increased in recent years. The criteria for candidate selection for lung retransplantation generally mirror the criteria used for selection for initial lung transplantation. Survival after lung retransplantation may have improved over time but remains inferior to survival seen after initial transplantation. For the individual patient, retransplantation should be analyzed as a time-dependent survival risk factor. Consideration must also be given to ethical issues surrounding lung allocation to retransplantation candidates.”

## **AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY/JAPANESE RESPIRATORY SOCIETY/LATIN AMERICAN THORACIC ASSOCIATION**

Evidence-based recommendations from the American Thoracic Society and three international respiratory/thoracic societies were published in 2011 for the diagnosis and management of patients with idiopathic fibrosis.<sup>[54]</sup> For appropriately selected patients with idiopathic pulmonary fibrosis, the group recommended lung transplantation (strong recommendation, low-quality evidence). An updated to this document was published in 2015 in which the committee did not make a recommendation regarding single versus bilateral lung transplantation in patients with idiopathic fibrosis.<sup>[55]</sup> The committee stated that "it is unclear whether single or bilateral lung transplantation is preferential for long-term outcomes".

## **GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE**

In 2017 the Global Initiative for Chronic Obstructive Lung Disease (GOLD) committee members performed a literature search and developed guidelines regarding the diagnosis, management and prevention of chronic obstructive pulmonary disease.<sup>[56]</sup> The committee

suggested that in carefully selected patients with COPD, lung transplantation has been shown to improve quality of life and functional capacity. The guidelines state:

“In selected patients with very severe COPD and without relevant contraindications, lung transplantation may be considered. ... Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, Pco<sub>2</sub> greater than 50 mm Hg or 6.6 kPa and/or Pao<sub>2</sub> less than 60 mm Hg or 8 kPa, and FEV<sub>1</sub> less than 25% predicted.”

These recommendations were made on the basis of evidence collected from observational studies; however, randomized controlled trials are unlikely in this patient population.

## SUMMARY

There is enough research to show that lung transplantation can improve survival in certain patients and thus may be considered medically necessary for patients when the policy criteria are met. It may be the only option for some patients with end-stage lung disease.

There is enough research to show that lung retransplantation can improve survival and may be the only option for patients with failed lung transplantation. Therefore, lung retransplantation may be considered medically necessary in selected patients who meet criteria for lung transplantation.

Lung or lobar lung transplantation or retransplantation is considered not medically necessary in all other situations when the policy criteria are not met.

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## CODES

Codes	Number	Description
CPT	32850	Donor pneumonectomy(ies) (including cold preservation), from cadaver donor
	32851	Lung transplant, single; without cardiopulmonary bypass
	32852	;with cardiopulmonary bypass
	32853	Lung transplant, double (bilateral, sequential, or en bloc); without cardiopulmonary bypass
	32854	;with cardiopulmonary bypass
	32855	Backbench standard preparation of cadaver donor lung allograft prior to transplantation, including dissection of allograft from surrounding tissues to prepare pulmonary venous/atrial cuff, pulmonary artery, and bronchus, unilateral
	32856	;bilateral
HCPCS	S2060	Lobar lung transplantation
	S2061	Donor lobectomy (lung) for transplantation, living donor

**Date of Origin:** March 2013